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HOMOZYGOUS HEMOGLOBIN C*

A New Hereditary Hemolytic Disease

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WASHINGTON, D. C.

FIVE separate types of human hemoglobin have been described.¶ These have been differentiated by variations in certain physicochemical properties.[2-5] They are classified according to the accepted system of nomenclature[6] as Type A (normal adult), S (sickle cell), F (fetal) and two more recently recognized abnormal varieties (C and D).¶

Types A, S and C hemoglobin are readily differentiated by relative mobilities in an electric field. The electrophoretic mobility of Type D hemoglobin is similar to that of Type S hemoglobin, from which it can be differentiated by solubility studies.[5] Type F hemoglobin has an electrophoretic mobility similar to that of Type A. Although paper electrophoretic separation of F hemoglobin from A hemoglobin is possible under special conditions[7] this is not feasible for quantitative purposes.[8] Type F hemoglobin, however, has previously been shown to differ from normal and Type C and S hemoglobin by its resistance to denaturation when introduced into an alkaline medium.[9] This property forms the basis for a simple quantitative test for F hemoglobin.[8]

The production of at least four types of human hemoglobin (A, S, C and D) appears to be under genetic control. All four have been described in various heterozygous combinations with the exception of CD. All hemoglobin forms have been described in the homozygous state with the exception of DD. Three cases of homozygous hemoglobin C disease[10-12] have been separately described by others.‖

The present report is concerned with detailed studies on a patient with homozygous hemoglobin C. Our results are correlated with the available findings on 3 others[10-12] to characterize further this newly recognized disease. The differential diagnosis and genetic features of hemoglobin C disease and the clinical significance of the C trait are discussed.

The subject of the present report has 64 living close relatives, including 9 living siblings, 5 of whom are half-siblings. Thirteen members of the family group were available and offered an excellent opportunity to study the genetic aspects of this disease in addition to the clinical and hematologic features.

MATERIALS AND METHODS

Filter-paper electrophoresis of hemoglobin was carried out as described previously.[8,13] Three per cent nondialyzed oxyhemoglobin solutions (0.01 cc.) were streaked on Whatman 3-mm. filter-paper strips. These were immersed in a Veronal buffer at pH 8.6 and ionic strength 0.05 in a plexiglass electrophoretic cell and run at 280 volts for four hours. A Heath–Kit power-supply unit served as the source of constant voltage. A self-recording photoelectric scanning device[14] was used to determine the amount of the various hemoglobin types present on the filter-paper strips.

The red-cell survival of the patient's cells in a normal recipient was studied by means of the Ashby technic.[15] Red-cell survival was also estimated by tagging of the patient's own cells with radiochromium.[16,17] The survival of normal red cells in the patient was determined by serial quantitative electrophoretic determination of the residual circulating normal (A) hemoglobin after transfusion into the homozygous C patient, as described below in the hematologic studies on the patient.

MN, Rh and ABO blood types were determined whenever possible to establish sibship or parenthood.

The patient's fecal urobilinogen was measured on a series of four-day collections marked with carmine dye according to the technic of Watson.[18]

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¶Another type of hemoglobin, hemoglobin E, was recently described by Itano.[1]

‖One of us (A.G.M.) recently identified another case of homozygous C disease. We know of at least 8 other cases of the disease in various parts of the country.

Fetal hemoglobin was determined by the method of Singer, Chernoff and Singer.[3]

The osmotic fragility of the patient's red cells was evaluated before and after incubation by the technic of Hunter,[19] slightly modified. Osmotic fragility before incubation was evaluated in all relatives who were studied.

Mechanical fragility[20] of the patient's red blood cells was calculated before incubation.

Case Report

E.P. (G.U.H. 41665), a 44-year-old Negress of West Indian ancestry, was first seen at Georgetown University Hospital Outpatient Department on July 10, 1952. Her complaints were weakness, fatigue and dyspnea on exertion. On questioning she reported intermittent pains in the knees, ankles, wrists and elbows since childhood and the more recent development of episodes of aching pains in the calves and forearms. There was intolerance to fatty foods. She had previously been treated unsuccessfully for anemia for 1 year.

Two of the patient's children had died in infancy of unknown causes. The 2 living children, both females, had a long history of frequent episodes of joint pains. One of the children was an achondroplastic dwarf. The patient's husband was not living.

She had been told, at the age of 14 years during one of her episodes of joint pain, that she had rheumatic heart disease. In 1936 x-ray study was reported as showing an enlarged heart. Six years later a cholecystotomy was performed for the removal of gallstones.

Physical examination revealed a well developed, well nourished woman without obvious skeletal defects or other deformities. The mucous membranes and nailbeds were moderately pale. There was no icterus and no significant adenopathy. The pupils were unequal in size and irregular and reacted sluggishly to light. There was minimal tortuosity of the retinal vessels. The apical beat of the heart extended 2 cm. to the left of the midclavicular line in the 6th intercostal space. There was no evidence of cardiac failure. The spleen was soft and extended to 7 cm. below the left midcostal margin on deep inspiration. The liver edge was felt 1 cm. below the right midcostal margin.

Other laboratory data included a consistently normal sedimentation rate, normal urine, negative stool guaiac tests, decreased gastric acidity, positive Kahn and positive treponema-immobilization tests, a negative tuberculin test, calcification of the ascending aorta consistent with syphilitic aortitis, an oral cholecystogram consistent with the presence of gallstones and normal roentgenograms of the skull, lower lumbar vertebras, pelvis and hands.

The patient's hematologic status was unchanged by therapy with iron by mouth and intravenously, cobalt, folic acid and vitamin B_{12}. She did not have febrile episodes or other evidence of infection. She was adequately treated for syphilis with penicillin, without any change in the over-all picture.

Hematologic Studies on the Patient

Blood studies revealed a moderate microcytic anemia (hematocrit of 31.5 per cent, hemoglobin of 11.2 gm. per 100 cc., red-cell count of 4,750,000, mean corpuscular volume of 66 cubic microns, mean corpuscular hemoglobin of 24 micromicrogm. and mean corpuscular hemoglobin concentration of 36 per cent). The reticulocyte count varied between 2 and 3 per cent. There was a moderate leukopenia (white-cell count of 4500) and a moderate thrombocytopenia (count of 123,000). The sickle-cell preparation (sodium metabisulfite) was repeatedly negative. The peripheral blood smear demonstrated the presence of approximately 30 per cent target cells, moderate numbers of fragmented red cells and an occasional nucleated red cell. There was some anisocytosis and poikilocytosis of the red cells. Generally the red cells appeared thin and pale and varied in diameter from 4 to 9 microns. There was no remarkable polychromatophilia (Fig. 1). Bone-marrow smears were moderately hypercellular and showed a relative increase in small basophilic normoblasts (metarubricytes). Evaluation of the unstained bone-marrow smear disclosed normal to slightly increased amounts of hemosiderin (Grade 3). The total serum bilirubin was 0.53 mg. per 100 cc. The direct Coombs test was negative. Platelet agglutinins could not be demonstrated.

Osmotic fragility of the red cells was moderately decreased before incubation and greatly decreased after 24 hours of sterile incubation (Fig. 2).

The mechanical fragility was slightly increased (9 per cent); normal values in our laboratory are 2 to 6 per cent.

An electrophoretic study of the patient's hemoglobin on April 4, 1953, revealed the presence of 100 per cent Type C hemoglobin (Fig. 3*B*). Fetal hemoglobin was less than 1 per cent.

An average of 7 determinations of the fecal urobilinogen excretion revealed an output of 335 mg. a day. The hemolytic index was 63 (normal, 10 to 20).

The blood volume by the radioactive chromium method[21] was 4600 cc. (71 cc. per kilogram of body weight). The red-cell mass was 1340 cc. (21 cc. per kilogram of body weight).

The survival time of normal red cells transfused into the patient was determined by an adaptation of the technic of filter-paper electrophoresis. At various intervals after transfusion hemoglobin solutions were prepared from the patient's blood and examined by paper electrophoresis. The transfused normal (A) hemoglobin was separated from the patient's C hemoglobin (Fig. 3*A*) and the percentage of each hemoglobin determined by the self-recording photoelectric scanner.[16] The amount of normal (A) hemoglobin remaining at various intervals after transfusion was plotted on a graph, which showed a straight-line decay of 106 days (Fig. 4). The mean red-cell survival of the patient's red cells in a normal recipient, determined by the Ashby technic, was 42 days. This indicated an intracorpuscular rather than an extracorpuscular hemolytic mechanism (Fig. 4).*

Studies on the Patient's Relatives

Thirteen close relatives of the patient were studied. They were interviewed and examined briefly, with special emphasis on palpation of the spleen and history of arthralgia. Blood was drawn from every person. All studies included routine hematologic evaluation, and, in most cases, paper electrophoresis, fetal-hemoglobin determination, osmotic fragility and blood typing were done. Four persons were examined for us by Captain Charles W. Butterworth, Jr., M.C., in Birmingham, Alabama, and the blood sent to us for hemoglobin electrophoresis. Blood typing, when done, was consistent with sibship or parenthood. Figure 5 shows the hemoglobin make-up of the patient's family.

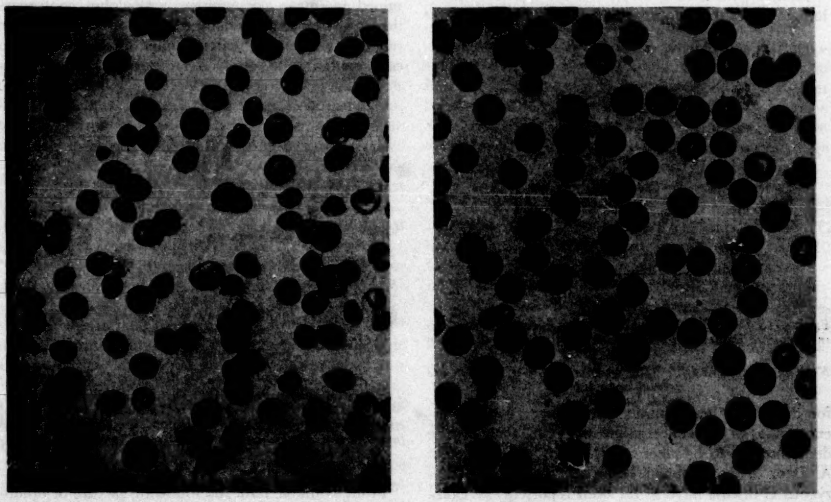
Only 2 of this group demonstrated homozygous Type A hemoglobin. These were a half-sister and a grandson whose mother was Type CA. Of the remaining 11, 9 were Type CA. Of these 9 with Type CA hemoglobin, 4 were full siblings of the propositus, 1 was a half-sister, 1 was the daughter of a half-sister, 1 was the daughter of a full-sister, and 2 were daughters. The 2 remaining members of the family, both grand-daughters of the propositus, were Type SA and CS. The latter, a 3-month-old infant, also demonstrated 30 per cent fetal hemoglobin — a normal finding at this age. Paper strips with hemoglobin electrophoretograms of the 6 heterozygous C carriers were examined by the photoelectric scanning device. The range of hemoglobin C varied between 34 and 40 per cent, with an average of 35.8 per cent (Fig. 3*C*). Fetal hemoglobin, which was determined in 5 persons with Type CA hemoglobin, was less than 1 per cent in each.

In 9 relatives with the heterozygous form of the disease

*Estimation of survival of the patient's red cells in her own circulation was done by tagging of 26 cc. of the patient's blood with 200 microcurie of radioactive chromium and transfusion of these cells back to her. The resulting survival-time curve revealed a half life of twenty-two days. (Half life of normal chromium-tagged cells in a normal recipient in our laboratory is twenty-four to thirty-six days.) Although the half life of the chromium-tagged patient's cells was shorter than normal the difference was not appreciable. The Ashby technic, on the other hand, clearly demonstrated significantly shortened red-cell life. This finding points out the limitations of the use of cells tagged with radioactive chromium to detect *mild* hemolytic states.

(CA) as well as in those with Type SA and CS hemoglobin, the osmotic fragility was reduced.

Reticulocyte counts, which were done in 3 persons with CA and in 1 with SC hemoglobin, were normal.



A B

FIGURE 1. *Peripheral Blood Picture (X600) of Homozygous C Patient* (A) *Compared with That of Her Daughter* (B), *Who Was Heterozygous C.*

Note the target cells and "folding over" of thin cells, producing "boat-shaped" forms in A *and the target cells in* B.

Sickling was demonstrated only in 2 persons demonstrating Type S hemoglobin by paper electrophoresis.

The peripheral blood smears of the relatives with Type CA hemoglobin revealed 6 to 40 per cent target cells (average

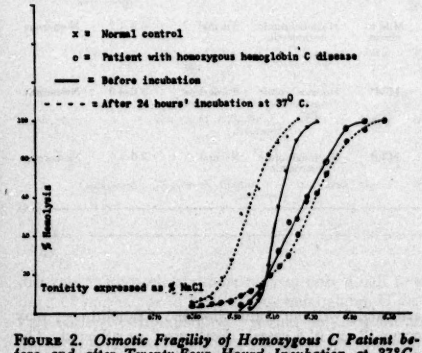

x = Normal control
o = Patient with homozygous hemoglobin C disease
= Before incubation
= After 24 hours' incubation at 37° C.
% Hemolysis
Tonicity expressed as % NaCl

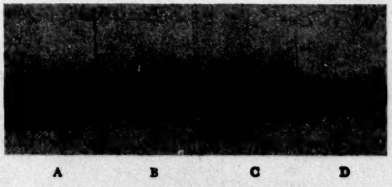
FIGURE 2. *Osmotic Fragility of Homozygous C Patient before and after Twenty-Four Hours' Incubation at 37°C., Compared with Normal Control.*

Note the increased resistance of hemoglobin C cells.

20 per cent) and occasional fragmented cells. The cells were normal in size and shape. No nucleated red blood cells were seen.

None of the relatives studied had either palpable livers or spleens.

Both daughters (Type CA hemoglobin) of the propositus had histories of "rheumatic fever," with frequent episodes



A B C D

FIGURE 3. *Paper Electrophoretograms.*

A = homozygous C patient after transfusion with normal blood (26 per cent HbA),

B = homozygous C patient without transfusion.

C = heterozygous hemoglobin C subject, daughter of patient (34 per cent C, 66 per cent A).

D = patient with sickle-cell trait (45 per cent S, 55 per cent A), granddaughter of patient.

of joint pains in the past. In neither case did physical examination reveal abnormal joint or cardiac findings. One niece (Type CA hemoglobin) also gave a history of frequent episodes of joint pains without evidence of heart disease or joint changes. The remaining relatives studied had no history of joint pain.

Discussion

Homozygous hemoglobin C disease is a new hematologic entity that requires hemoglobin electrophoresis for diagnosis. The characteristic defect is the presence of a single abnormal hemoglobin that can be demonstrated to be electrophoretically different from A, D or S hemoglobin. Three other cases of homozygous C disease have so far been reported.[10-12] Complete data are available for 2 of these patients.[10,11] In a comparison of these cases with our patient the clinical and hematologic findings are in general agreement except for the presence of arthralgia (Table 1). The type of anemia seen in our patient was consistently normochromic and microcytic (reduced mean corpuscular volume and mean corpuscular hemoglobin and normal mean corpuscular hemoglobin concentration) whereas that in the other 3 patients was normochromic and normocytic. The hypochromic appearance of some erythrocytes in these patients in the presence of normal hemoglobin concentration (as determined by mean corpuscular hemoglobin concentration) may be explained by the predominance of thin red cells. A similar phenomenon is seen in sickle-cell anemia.

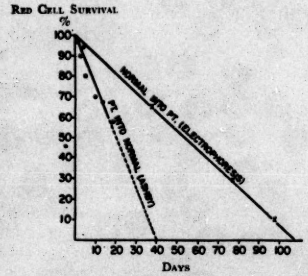


Figure 4. *Graph of Survival Time of Patient's Red Cells in a Normal Recipient (Ashby Technic) and Normal Cells in the Patient.*

Note the diminished life span of homozygous C cells in the normal recipient.

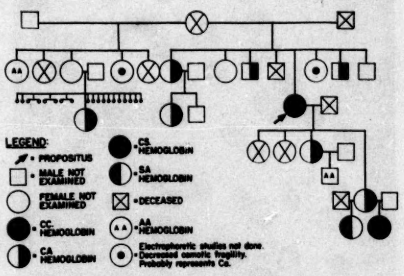


Figure 5. *Family Study of the Patient's Relatives.*

The small symbols on the right signify unavailable relatives. Note that both children of different husbands of the propositus's daughter carry S hemoglobin, indicating that both fathers must have had either sickle-cell anemia or sickle-cell trait.

From available data the following picture of homozygous hemoglobin C disease emerges. There is mild hemolytic anemia, with splenomegaly and variable arthralgia without joint changes. Cholelithiasis may occur (2 out of 4 cases). Both sexes are affected. The disease has been documented so far only in the American Negro‡ and does not appear to shorten life expectancy since several patients have been middle-aged. The peripheral blood smear, in addition to

Table 1. *Clinical and Hematologic Characteristics of Homozygous Hemoglobin C Disease.*

Case No.	Source	Age	Sex	Race	Splenomegaly	Arthralgia	Anemia	Type of Anemia	Serum Bilirubin	Reticulocytes	Target Cells
		yr.								%	
1	Spaet et al.[10]	5	M	N	Present	Absent	Mild to absent	Normochromic normocytic	Normal	0.8–1.2	Numerous
2	Ranney et al.[11]	35	F	N	Present	Present	Mild*	Normochromic normocytic	Borderline elevation†	3.0–4.0	Numerous
3	Present study	43	F	N	Present	Present	Mild‖	Normochromic microcytic	Normal	2.0–3.0	Numerous

*Hemoglobin of 10-12 gm. per 100 cc.
†1.2 mg. per 100 cc.
‡9-11 per cent.
‖Hemoglobin of 11.5–12.5 gm. per 100 cc.
¶9 per cent.

‡Except for a case in a sixteen-year-old boy of Sicilian origin reported by Kraus and his associates.[12]

numerous target cells, fragmented cells, anisocytosis and poikilocytosis, may show small numbers of nucleated red cells. The presence of a significant number of target cells has been a constant feature in all cases studied. Reticulocytosis is mild or may be absent. Erythroid hyperplasia of the bone marrow was observed in all 4 cases. Serum bilirubin is normal or slightly elevated. Fecal urobilinogen determinations, when performed, have revealed increased values. The red cells show increased resistance to hypotonic saline solution. This finding is accentuated after sterile incubation of the blood at 37°C. for twenty-four hours (Fig. 2). Mechanical fragility is mildly increased. The sickling test is negative. The amount of fetal hemoglobin is within normal limits.

The mechanism by which the presence of hemoglobin C leads to anemia is not clear. Ashby measurements of survival time, showing a shortening of survival of the patient's cells to forty to fifty-five days[10] and a normal survival of normal red cells in the case reported above, point to an intracorpuscular hemolytic mechanism (Fig. 4). The increased mechanical fragility of erythrocytes with 100 per cent hemoglobin C may have some effect on their premature removal from the circulation.

However, increased hemolysis alone cannot be the entire explanation for the anemia of homozygous hemoglobin C disease. An uninhibited bone marrow can compensate for an increased rate of hemolysis by increasing its hemoglobin output five or six times the normal rate.[23] Red-cell-life shortening of only a half to a third of normal, as in homozygous hemoglobin C disease (forty to fifty-five days), should only require an increase of two or three times the normal hemoglobin production. The presence of anemia in these patients, therefore, represents failure of the bone marrow to respond normally to a mild increase in the rate of hemolysis and indicates a reduction in the reactive capacity of the bone marrow. Similar observations have been made in sickle-cell and Mediterranean anemia,[23] in which red-cell life is shorter, however, so that the anemia is more severe. The possible role of the spleen in this type of marrow inhibition is now under investigation by two of us (D.W.T. and C.E.R.).

Little information about the physicochemical properties of hemoglobin C is available. Its solubility in buffered phosphate is higher than that of any other hemoglobin.[24] The ultraviolet absorption spectrum in a Beckman DU spectrophotometer and the sedimentation constant determined with the ultracentrifuge are identical with those of normal hemoglobin.[11]

C Trait

In the heterozygous carriers (C trait) studied C hemoglobin was found as the minor component (30 to 40 per cent), and a normal (A) hemoglobin as the major component (60 to 70 per cent) on electrophoretic examination.[25,26] In this respect the condition resembles the sickling trait, in which 25 to 45 per cent sickling (S) hemoglobin is found together with larger amounts of A hemoglobin. Hemoglobin C trait is manifested by the presence of target cells and occasional fragmented cells.[7,11,25,26] Variation in shape and size of the cells, if present, is very slight. Osmotic resistance is usually increased. Nucleated red cells are not seen. Reticulocyte counts are normal, and determinations of red-cell life reveal a normal life span.[26,27]

Three of the C trait patients discussed above and another with C trait observed elsewhere complained of moderately frequent episodes of joint pains and aching bones. Since the homozygous hemoglobin C condition is frequently associated with arthralgia a similar finding in the heterozygous C trait carriers may be significant. Further careful observations are needed.

TABLE 1 *(Concluded).*

Case No.	Nucleated Red Cells in Peripheral Blood	Osmotic Fragility	Mechanical Fragility	Fecal Urobilinogen	Sickling	Bone Marrow	Electrophoresis of Hemoglobin	Alkaline Denaturation	Hemoglobin Abnormality in Offspring	Life Span of Normal Red Cells in Patient	Life Span of Patient's Red Cells in Normal Recipient
							%HbC	*%FHb*		*days*	*days*
1	Occasional	Decreased	Normal	Increased	Absent	Normoblastic hyperplasia	100	<1	—	—	55
2	—	Decreased	Slightly increased‡	—	Absent	Normoblastic hyperplasia	100	<1	4 children; all C trait (CA).	—	—
3	Occasional	Decreased	Slightly increased¶	Increased	Absent	Normoblastic hyperplasia	100	<1	2 children; both C trait.	106 (normal)	42

Genetic Considerations

The genetic data of this family and those reported by others[7,11,12,25,26] show that the inheritance of hemoglobin C is determined by a gene whose effect can be

demonstrated in both homozygous and heterozygous states by electrophoretic examination of hemoglobin. It is postulated[26,28] that presence of the gene for hemoglobin C on 2 allelic chromosomes produces homozygous hemoglobin C disease, whereas the effect of this gene on only 1 of the 2 chromosomes results in the heterozygous hemoglobin C trait. Transmission of these genes appears to follow the law of simple Mendelian inheritance without any evidence of sex linkage. The genetic background of hemoglobin C, therefore, resembles closely that of sickling hemoglobin, and

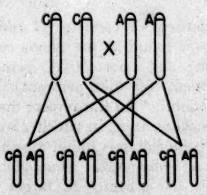


FIGURE 6. *Genetic Scheme of a CC x AA Mating.*
Note that with an independent assortment of chromosomes, all children will be CA type.

homozygous hemoglobin C disease is the genetic counterpart of sickle-cell anemia.

Our genetic findings and other data of families with CS combination best fit the hypothesis[28] that the hemoglobin C gene is a multiple allele of the genes controlling normal (A) and sickling (S) hemoglobin production and thus occupies the same locus on a chromosome pair. Alternate genetic explanations[26] are as follows: close linkage of the various genes controlling the production of different types of hemoglobin and the location of the hemoglobin C gene on a different chromosome. Although neither possibility has yet been ruled out, owing to lack of sufficient data (especially results of CS x AA mating to prove or disprove the latter theory*), the multiple allele theory is the best working hypothesis compatible with all data at present.

This hypothesis allows prediction of possible hemoglobin abnormalities in offspring and relatives by simple genetic shuffling based on independent combination of chromosomes. An example is presented in Figure 6, which demonstrates the possible coupling of chromosomes in a mating of a homozygous C patient with a normal person. The diagram shows that all offspring of such a union are heterozygous carriers of hemoglobin C. This was found to be actually true. Both children of our homozygous C patient and 4 offspring of the patient described by Ranney et al.[11] were carriers of the C trait.

Further hemoglobin combinations in offspring of abnormal hemoglobin carrier matings are illustrated by genetic checkerboards in Figures 7 (CA x CA), 8 (CA x AA), 9 (CA x SA), 10 (CC x SA) and 11 (CC x CA). It should be pointed out that the offspring ratios for the matings listed will also be true if the alternate genetic hypotheses of "close linkage" or "different chromosomal location" ultimately prove to be correct. Children of CS x AA and CS x CA matings are not shown in the diagrams since ratios would differ, depending on whether the "multiple allele" or "different chromosome location" theory proves to be the correct one. Further extensive family studies are required to validate the exact percentage distribution of persons with different hemoglobin types among offspring of the various matings.

	C	A
C	CC	CA
A	CA	AA

FIGURE 7. *CA x CA Mating.*
Note that 25 per cent of offspring are homozygous C and normal (AA) respectively and 50 per cent C trait.

	A	A
C	CA	CA
A	AA	AA

FIGURE 8. *CA x AA Mating.*
Note that 50 per cent of offspring are C trait and 50 per cent normal (AA).

	S	A
C	CS	CA
A	SA	AA

FIGURE 9. *CA x SA Mating.*
Note that 25 per cent of offspring are C trait, 25 per cent are sickling trait, 25 per cent sickling hemoglobin C disease and 25 per cent normal (AA). This type of mating represents the usual genetic background of CS patients.

	S	A
C	SC	CA
C	SC	CA

FIGURE 10. *CC x SA Mating.*
Note that 50 per cent of offspring are C trait and 50 per cent sickle hemoglobin C disease. In one such mating reported[28] the actual frequency in 3 children was 2 CA and 1 SC.

	C	A
C	CC	CA
C	CC	CA

FIGURE 11. *CA x CC Mating.*
Note that 50 per cent of offspring are homozygous C disease and 50 per cent are C trait.

*CS offspring of such a union would prove that the C hemoglobin gene is located on a different chromosome.

Figure 7 shows that the union of 2 C trait carriers will produce homozygous hemoglobin C disease in 25 per cent, the C trait in 50 per cent and normal hemoglobin (AA) in the remaining 25 per cent of the children. Although hemoglobin analysis of both parents of homozygous hemoglobin C patients has not yet been reported, it is likely that in most cases the father and mother are C trait carriers (CA). It is also apparent that the rare matings of CS x CA, CC x CA and CC x CS may produce homozygous hemoglobin C offspring.

The incidence of hemoglobin C in a study of 500 Negro patients in a Baltimore clinic[7] selected at random was 2 per cent (CA 1.8 per cent and CS 0.2 per cent). Another study[29] reports a value of 2.9 per cent for hemoglobin C. Except in 1 family[22] hemoglobin C has not been detected in white patients. Assuming random mating of the Negro population for hemoglobin type the frequency of marriages involving the various hemoglobins can be calculated. The ratios of children with different hemoglobin composition can then be readily determined by means of the genetic scheme described above. The approximate frequency of homozygous C and CS may thus be readily ascertained.

It was shown above that the mating of parents of homozygous hemoglobin C patients is usually of the CA x CA or rarely of the CS x CA type. By means of a value of 2.5 per cent for the incidence of the C trait it can be calculated* that the probability of a CA x CA mating in the Negro population is 6.25 in 10,000 marriages. Since 25 per cent of the offspring of a CA x CA mating will be of the CC type the number of homozygous C children will be 15.6 per 100,000 Negro population.† Similar calculations‡ for the rare CA x CS mating using a frequency of 0.13 per cent for CS (as described below) give a figure of 1.6 homozygous C offspring per 100,000 Negro population (or 0.8 per 100,000 if the "different chromosome location" theory is correct). The addition of 15.6 and 1.6 gives an estimated occurrence of homozygous hemoglobin C of 17.2 per 100,000 Negro population, or 0.0172 per cent. Since the Negro population of the United States is nearly 15,000,000 the number of homozygous C patients should be approximately 2500 or *1 in 6000 Negroes.*

Similar calculations based on a sickling-trait (SA) prevalence of 10 per cent indicate that the frequency of sickle-cell hemoglobin C disease (CS) is about 0.13 per cent, or approximately half that of sickle-cell anemia. The discrepancy between this figure and the finding of only 3 CS patients in 48 persons with sickle-cell disease studied by Neel et al.[30] is probably explained by the fact that many patients with sickle-cell hemoglobin C disease are only mildly affected and do not come to the attention of a physician.

The calculated occurrence of CC and CS must be considered a preliminary estimate for an understanding of the size of the problem. Further extensive population surveys for hemoglobin types will be necessary for complete validation of the calculations presented above.

*$\frac{25}{100} \times \frac{25}{100} = \frac{625}{10{,}000}$, or 6.25 in 10,000.

†$\frac{625}{10{,}000} = \frac{4}{100} = \frac{0.0156}{100}$ CC.

‡Probability of CA x CS mating is $2 \times \frac{25}{100} \times \frac{13}{100} = \frac{65}{10{,}000}$

since 25% of such matings will be CC: $\frac{65}{10{,}000} = \frac{4}{100} = \frac{0.0016}{100}$ CC offspring.

Differential Diagnosis

The finding of normal to increased amounts of hemosiderin[31] in the bone marrow may be of help in the differentiation of homozygous hemoglobin C disease from iron-deficiency anemia, which is sometimes accompanied by target cells.

Homozygous hemoglobin C disease must be distinguished mainly from thalassemia minor. Target cells and increased osmotic resistance of red cells are found in both conditions. However, significant true hypochromia, as well as stippling and erythrocytosis, has been found only in thalassemia. Diagnostic criteria for differentiation of the hemoglobin C trait, hemoglobin C disease, thalassemia minor and thalassemia major are listed in Table 2. Definite differentiation requires electrophoretic examination of hemoglobin.

The various types of sicklemia, such as sickling trait, sickle-cell anemia, sickle-hemoglobin C disease and sickle-thalassemia disease (microdrepanocytosis) [7,8,30] can be differentiated from hemoglobin C trait and hemoglobin C disease by the negative sickling test and the absence of S hemoglobin on electrophoresis in hemoglobin C trait and hemoglobin C disease. Sickle hemoglobin C disease and sickle thalassemia disease may give diagnostic difficulties because of the large number of target cells in these conditions.

Target cells found after splenectomy, after hemorrhage, with dehydration and with liver disease and obstructive jaundice should cause few diagnostic difficulties.

Since hemoglobin C abnormalities may simulate the hematologic picture of thalassemia the diagnosis of previously reported cases of Mediterranean disease in the Negro has been questioned. One of us (A.G.M.) recently observed a Negro family with classic thalassemia but no hemoglobin C on electrophoretic hemoglobin analysis. This finding demonstrates that true thalassemia actually does occur in the Negro.

The arthralgia of hemoglobin C disease may be confused with joint symptoms seen in rheumatic fever, rheumatoid arthritis, sarcoidosis and lupus erythematosus. Rheumatoid arthritis is differentiated by the eventual development of chronic joint deformity, which does not occur in hemoglobin C syndromes.

The characteristic lymph-node lesions usually differentiate sarcoidosis. Other clinical features and the characteristic L.E. cell are generally found in lupus erythematosus. An elevated sedimentation rate and antiresistance. Arthralgia was observed in 3 of our patients with C trait.

Genetic study of this patient's family and other data show that the inheritance of hemoglobin C simi-

TABLE 2. *Differential Diagnosis of Hemoglobin C Disease and Thalassemia.*

DIAGNOSIS	RACE OF PATIENT	USUAL GENETIC MAKE-UP OF PARENTS	SPLENOMEGALY	ARTHRALGIA	ANEMIA
C trait (CA)	Negro	1 C trait; 1 normal.	Absent	May be present	Absent
Homozygous hemoglobin C	Negro	Both C trait	Usually present	Often present	Mild
Thalassemia minor	Mediterranean; Negro; Chinese; Thai.	1 with thalassemia minor; 1 normal.	May be present	Absent	Absent to moderate
Thalassemia major	Mediterranean; Negro; Chinese; Thai.	Both with thalassemia minor	Usually marked	Absent	Severe

*0—1.7 per cent.
†40—100 per cent.

streptolysin titer and electrocardiographic abnormalities may help in the differential diagnosis of rheumatic fever. Target cells are not seen in any of the diseases mentioned above, and the electrophoretic hemoglobin pattern of hemoglobin C is pathognomonic.

SUMMARY AND CONCLUSIONS

Homozygous hemoglobin C disease is a recently identified hereditary hemolytic disorder characterized by the presence of 100 per cent hemoglobin C. Hemoglobin C is an abnormal hemoglobin electrophoretically different from normal (A), fetal (F), sickling (S) and D hemoglobin.

A case of the disease in a forty-four-year-old Negress is described. Detailed hematologic and family studies are reported and compared with data on 3 previously described homozygous hemoglobin C patients.

Homozygous hemoglobin C disease occurs in Negroes of both sexes. Splenomegaly is usually present. Arthralgia and cholelithiasis are variable findings. The characteristic hematologic features are as follows: mild normochromic, normocytic to microcytic anemia; many target cells and occasional nucleated red cells in the peripheral blood; increased osmotic resistance of red cells to hypotonic saline solution; normal number to mild elevation of reticulocytes; normal to slightly elevated serum bilirubin; normoblastic hyperplasia of the bone marrow; an intracorpuscular hemolytic defect with an erythrocyte life span of forty to fifty days; and a characteristic electrophoretic pattern of hemoglobin.

The C trait is not associated with hematologic abnormalities besides target cells and increased osmotic lar to that of hemoglobin S is determined by a gene whose effect can be demonstrated by hemoglobin electrophoresis in both the heterozygous and the homozygous state. Presence of the gene for hemoglobin C on 2 allelic chromosomes presumably produces homozygous hemoglobin C disease whereas a single dose of the gene appears to result in the heterozygous C trait. All data fit the hypothesis that the gene controlling hemoglobin C synthesis occupies the same chromosomal locus as the genes for hemoglobin A and hemoglobin S.

Calculations based on the approximate occurrence of the C trait in the Negro population (2.5 per cent) suggest a frequency of homozygous hemoglobin C disease of 0.0172 per cent or 1:6000 Negroes.

Hemoglobin C disorders must be differentiated from thalassemia minor and other conditions associated with target cells. Hemoglobin electrophoresis is required for definite differentiation.

Homozygous hemoglobin C disease should be considered in all cases of unexplained anemia, obscure arthralgia and idiopathic splenomegaly in the Negro.

Studies of turnover of radioactive iron revealed a half-disappearance time of 1.25 hours, a plasma iron turnover rate of 0.59 mg. per kilogram per day, a red-cell uptake of 60 per cent at two weeks, a red-cell iron turnover of 0.36 mg. per kilogram per day and a calculated turnover of red-cell mass of 1.7 per cent per day. The serum iron was 85 microgm. per 100 cc. These studies were done by two of us (C.R. and D.T.) in collaboration with Dr. Ralph Peterson, of the National Institutes of Health.

Ten days after the institution of cortisone therapy the serum iron had increased to 174 microgm. per 100 cc., and the hematocrit to 35.5 per cent. At that time the half-disappearance time of radioactive iron was 1.42 hours, the plasma iron turnover rate was 0.81 mg. per kilogram per day, the red-cell uptake of radioactive iron was 80 per cent in two weeks, the red-cell iron turnover was 0.65 mg. per

kilogram per day and the calculated turnover of red-cell mass was 2.9 per cent per day.

Because of the observation that venous blood on standing remained bright red for several days longer than control blood and the possible implications of this observation so far as this patient's mental symptoms and arthralgias were concerned, an oxygen dissociation curve was done. This was found to be normal. In addition the ultraviolet absorption spectrum was normal.

TABLE 2 *(Concluded).*

Hypochromia & Microcytosis	Target Cells & Increased Osmotic Resistance	Nucleated Red Cells	Hemoglobin Analysis		
			Hemoglobin C	Hemoglobin A	Fetal Hemoglobin
			%	%	
Absent	± to +++	Absent	30-40	60-70	Normal amounts*
No hypochromia; microcytosis variable.	+++	+	100	—	Normal amounts*
Mild to moderate	+ to ++	Usually absent	—	Variable	Variable increases
Severe	+ to +++	+++	—	0-60	Increased amounts†

We are indebted to several investigators, who aided greatly in some aspects of this study: Lieutenant Colonel William Crosby and Captain James W. Hollingsworth, of Walter Reed Army Medical Center, and Ralph Peterson and Daniel Tosteson, of the National Institutes of Health.

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PULMONARY TUBERCULOSIS IN NORTHERN NEWFOUNDLAND AND LABRADOR*

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THE death rate from pulmonary tuberculosis has dropped sharply in the past few years. Health education, with increased hospital beds for the care of patients as well as modern pulmonary surgery and chemotherapy, has been responsible for reduction in mortality and morbidity, to the point where the rate in Canada has now dropped to 18 per 100,000 population.

Newfoundland has the highest death rate for pulmonary tuberculosis of any province of Canada, and the disease is still the leading cause of death, with a recorded death rate for the province in 1953 of 46.8 per 100,000 population. High as this rate is, much has been done to control tuberculosis since Newfoundland became the tenth province of Canada five years ago: in 1948 the figure was 154 per 100,000, or more than three times the present rate.

The Grenfell Mission is a medical mission to the people of Northern Newfoundland and Labrador, comprising the electoral districts of White Bay, St. Barbe and Labrador. Tuberculosis, with a very high death rate in these districts, has constituted the main medical problem. The recorded rates in these districts since 1941 are shown in Table 1.

Recorded death rates do not give a true picture of the prevalence of a disease. However, significant drops in mortality rates show control. Some indication of the frequency of tuberculosis is given by a survey conducted by the Newfoundland Tuberculosis Association in co-operation with the Grenfell Mission in Northern Labrador in the summer of 1951. All the inhabitants living from Hamilton Inlet to Hebron were examined by chest roentgenograms; 804 persons were studied. On the basis of these films 68, or 8.4 per cent, were regarded as having *active* tuberculosis. Ninety-six per cent of the population over five years of age were surveyed.

In 1927 the Grenfell Mission built at St. Anthony, on the Northern tip of Newfoundland, a new modern general hospital of 80 beds with an annex of 20 beds for the treatment of pulmonary tuberculosis. Since that time patients with pulmonary tuberculosis have been admitted and treated. Previously, once a case was diagnosed, the patient was usually discharged from the hospital, this being the common practice in most hospitals in the province.

METHODS

This study analyzes and follows up all the patients with pulmonary tuberculosis admitted to and discharged from the hospital from 1927 to August, 1952, inclusive, and correlates the results obtained with the evolution of the modern approach to the treatment of tuberculosis. Admissions are broken down into five periods for simplicity. During the last period, from 1947-52, treatment changed radically. Chemotherapy and streptomycin, later combined with PAS, as well as some definite surgical procedure rather than bed rest, constituted the treatment of choice.

From 1927 through 1952 there were 1064 admissions for 830 cases of pulmonary tuberculosis. Follow-up studies were not possible in 102 of these patients, many of whom must be presumed dead.

Seventy-eight, or 9.4 per cent, had some other form of tuberculosis as a complication of the pulmonary disease. These included bone and joint, meningeal, genitourinary and intestinal tuberculosis, and in some cases a combination of several.

TABLE 1. *Death Rates from Tuberculosis in Districts Served by the Grenfell Mission.*

DISTRICT	RATE IN 1941 *per 100,000*	RATE IN 1947 *per 100,000*	RATE IN 1950 *per 100,000*	RATE IN 1953 *per 100,000*
St. Barbe	364	75	95	102
White Bay	167	61	93	22
Labrador	200	300	169	58

The admissions in these periods, with the final outcome, are demonstrated in Table 2. Significant changes are apparent in the last group, in which there were more readmissions. This represents a better follow-up total of patients with old cases, who were readmitted to the hospital for definite treatment, and also re-examination of some arrested cases. The most striking improvement was apparent in the number alive and well, with apparently arrested disease in this group. Sixty-six per cent of the patients admitted in this period were known to be alive and well when seen at follow-up examination as against 7.8 per cent now alive and well of those admitted in the first period from 1927-31. Undoubtedly the shorter follow-up period in the last group accounts for part of the improvement, but deaths in hospital were proportionately lower.

STAGE OF TUBERCULOSIS

The classification of disease in these periods is shown in Table 3. The largest number of cases in all periods were far advanced. Only during the last period were many patients with minimal cases admitted. This is a direct result of surveys carried out by the Newfound-

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 19, 1954.

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land Tuberculosis Association and by the Grenfell Mission by means of boats equipped with x-ray units.

Treatment

The treatment given during these periods is presented in Table 4. Bed rest alone as the method of treatment dropped from 90 per cent of patients admitted in the first period to 21 per cent in the last. When this last period is further examined it is apparent that no new patients with active disease and positive sputum have received bed rest only since 1950. With the decrease in bed rest surgery proportionately increased. In the last period this was chiefly thoracoplasty or phrenic-nerve crush combined with chemotherapy.

The first procedures undertaken apart from bed rest were pneumothorax and phrenic-nerve crush, the former being used slightly more frequently from 1927 to 1946. In the last five-year period the use of pneumothorax dropped, and in the last two years no new pneumothoraxes were induced (Table 5).

The results of pneumothorax were only fair, and follow-up studies on the early cases, from 1927 to 1941, showed a poor outcome. Only 2 patients out of 25 treated by pneumothorax during 1932 to 1936 are alive today. Of the 89 throughout the whole period who received pneumothorax for periods varying from six months to three years only 30, or 34 per cent, are alive and well. Twenty-one of these were treated in the last ten years studied; the follow-up period was shorter. The majority received some form of treatment besides pneumothorax. Five patients are alive with chronic tuberculosis.

Phrenic-nerve crush proved of value especially as

Table 2. *Admissions and Final Outcome.*

Period	No. of Admissions	Patients Alive and Well	Patients Alive with Tuberculosis	Deaths from Tuberculosis	Deaths from Other Causes	Patients with No Follow-up Study
1927-31	128	10	7	84	1	26
1932-36	166	22	5	119	0	20
1937-41	266	55	23	174	0	14
1942-46	203	62	24	103	2	12
1947-53	301	201	27	39	4	30
Totals	1064	350	86	519	7	102

Table 3. *Classification of Disease on Admission.*

Period	Far Advanced Bilateral Disease	Far Advanced Unilateral Disease	Moderately Advanced Bilateral Disease	Moderately Advanced Unilateral Disease	Miliary Tuberculosis	Minimal Tuberculosis	Childhood Tuberculosis	Arrested Tuberculosis
	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases
1927-31	74	9	6	14	0	0	0	0
1932-36	95	11	11	27	15	2	1	0
1937-41	138	16	31	29	9	27	4	10
1942-46	92	11	54	7	6	19	10	9
1947-52	111	31	37	39	12	71	12	13
Totals	510	78	139	116	42	119	27	32

Table 4. *Types of Treatment.*

Period	Bed Rest Only	Thoracoplasty	Pneumothorax	Phrenic-Nerve Crush	Pneumoperitoneum	Extrapleural Pneumoperitoneum	Streptomycin	Resection
	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases	No. of cases
1927-31	115(90%)	2	2	0	0	0	0	0
1932-36	103(62%)	1	25	21	0	0	0	0
1937-41	189(71%)	8	28	20	0	3	0	0
1942-46	121(59%)	6	24	27	0	1	0	0
1947-52	65(21%)	62	10	51	17	7	82	8
Totals	593	79	89	119	17	11	82	8

an adjunct to other forms of therapy. It was used frequently in the last period, particularly in the preparation of the patient for further definitive surgery, especially thoracoplasty, or in combination with chemotherapy. The results are presented in Table 6.

Sixty out of 119 patients, or 50 per cent of those treated over the years by phrenic-nerve crush, are alive and well today.

In the last five years studied, thoracoplasty was carried out whenever possible, and the number of cases so treated increased considerably (Table 7).

Bilateral disease did not contraindicate thoracoplasty. Patients were prepared by chemotherapy, phrenic-nerve crush, pneumoperitoneum and bed rest.

When the disease gave signs of stabilizing on x-ray and clinical evaluation a modern standard procedure was carried out on the worse side, 6 to 9 ribs being removed in stages—2 ribs at a time. The inferior angle of the scapula was excised routinely in a 6-rib thoracoplasty. All the rib, including the head and the transverse process of the vertebra and, in the upper ribs, the costal cartilage to the sternum, was removed.

Results

The results are gratifying. After operation many bilateral cases showed complete clearing on the side less involved, with stable, arrested disease on the operated side. Many patients were salvaged in this procedure. In the last five-year period, the sputum was converted to negative in 83 per cent. Of 79 patients who underwent thoracoplasty 12 died in the hospital or after discharge, and 5 still have chronic active disease. Five more were not available for follow-up study. The remaining 57, or 72 per cent, are known to be alive, well and working.

During the last period studied 82 patients received chemotherapy. At first this was a short course of streptomycin daily. Later, it was changed to biweekly

Table 5. *Results of Follow-up Study Six Months to Three Years after Pneumothorax.*

Period	No. of Cases	Patients Alive & Well	Patients Dead of Tuberculosis	Patients Alive with Tuberculosis	Patients with Complications	Patients Treated with Pneumothorax	Patients Not Available for Follow-up Study
1927-31	2	1	1	0	1	2	0
1932-36	25	2	20	1	4	6	2
1937-41	28	6	19	0	14	16	3
1942-46	24	14	6	4	15	12	0
1947-52	10	7	3	0	5	2	0
Totals	89	30	49	5	39	38	5

Table 6. *Results of Phrenic-Nerve Crush.*

Period	No. of Patients	Patients Treated with Phrenic-Nerve Crush Alone	Patients Alive & Well	Patients Alive with Chronic Tuberculosis	Patients Dead of Tuberculosis	Patients Not Available for Follow-up Study
1927-31	0	0	0	0	0	0
1932-36	21	9	4	1	14	2
1937-41	20	17	5	1	15	4
1942-46	27	14	8	3	15	1
1947-52	51	16	43	3	4	1
Totals	119	56	60	8	48	8

Table 7. *Results of Thoracoplasty.*

Period	No. of Patients	Patients Alive & Well	Patients Alive with Tuberculosis	Patients Dead in Hospital	Patients Dead Since Discharge	Patients with Conversion of Sputum	Patients Not Available for Follow-up Study
1927-31	2	0	0	1	1	0	0
1932-36	1	0	0	0	0	0	1
1937-41	8	5	0	0	3	5	0
1942-46	6	0	3	2	1	0	0
1947-52	62	52(83%)	2	2	2	52	4
Totals	79	57(72%)	5	5	7	57	5

administration with PAS for longer periods. Forty-one patients received chemotherapy before and after thoracoplasty; the remaining 38 did not.

Also, during the last period, 8 resections were carried out. These included lobectomies and segmental and subsegmental resections. Indications were cavernous lesions that remained open or inspissated cavities.

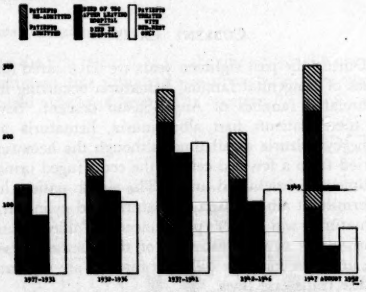

FIGURE 1. *Over-All Results of Therapy.*

The results in all 8 cases were good. Chemotherapy, consisting of streptomycin and PAS, was given in all cases. All patients are alive and well, with negative sputums and apparently arrested disease. Since 1952 resections have been carried out extensively, with broader indications.

The over-all results during the years are presented in Figure 1.

It is apparent that the results are fairly consistent from 1927 to 1946. Approximately 60 per cent of the patients either died in the hospital or of pulmonary tuberculosis after discharge. In the last period the mortality dropped to 12 per cent. Furthermore, if this last period is divided from 1950 to 1952, only 1.5 per cent of patients have died.

This decrease in mortality parallels the use of chemotherapy with modern surgery, with a reduction not only in mortality but also in morbidity.

DISCUSSION

The tuberculosis situation in Newfoundland is still grave. But remarkable progress has been made in a few years. There are still many problems, a major one being the rehabilitation of patients who are fishermen or lumbermen living a rugged life under marginal economic conditions. But the situation is rapidly appearing brighter, and hope and optimism seem warranted.

SUMMARY

The death rate from tuberculosis in Newfoundland is still the highest of any province of Canada.

Labrador has the highest rate in Newfoundland. A survey showed a frequency of 8.4 per cent of active pulmonary tuberculosis in a group over five years of age.

The results of treatment of 830 patients with 1064 admissions of pulmonary tuberculosis studied at the Grenfell Mission Hospital from 1927 to 1952 are analyzed.

CONGENITAL HEREDITARY HEMATURIA

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THE purpose of this paper is to emphasize a congenital hereditary syndrome characterized primarily by hematuria and often accompanied by nerve deafness. It is important that this condition be distinguished from acute or chronic glomerulonephritis because of its different etiology, course and prognosis.

REVIEW OF LITERATURE

In 1901 Attlee[1] described a family in which the father died of uremia at thirty years of age and 3 daughters were observed at five, four and two years of age to have recurrent attacks of gross hematuria associated with malaise and pyrexia. In the intervals between attacks the children appeared to be healthy, but the urine always contained albumin, red blood cells and granular casts.

Guthrie,[2] in 1902, investigated a family that was restudied by Kendall and Hertz[3] in 1912, by Hurst[4] in 1923 and by Alport[5] in 1927.

Figure 1 gives a résumé of the occurrence of this syndrome in members of the family studied by these authors. Males appeared to be more seriously affected than females. Of the 28 members of this family, 15—7 males and 8 females—were afflicted with the disease. Of the 7 males 5 died between four and nineteen years of age, and 2 were alive at thirteen and fifteen years. Of the females only 1 had died at the age of twenty-four years, the others having attained the ages of ten, thirty-five, thirty-six, thirty-seven, forty-two and sixty-four years.

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Hematuria, cylindruria and albuminuria were found in the affected persons examined in infancy, apparently persisting continuously but varying in degree. Infection, with or without fever, was associated with exacerbations of the hematuria and at times with abdominal pain and vomiting. Such exacerbations were less frequent after the first decade of life. Guthrie[2] made a special note of the fact that the patients he observed for seven years appeared to be in good health, with no signs of chronic nephritis. Reinvestigation twenty-one and twenty-five years later[4,5] showed

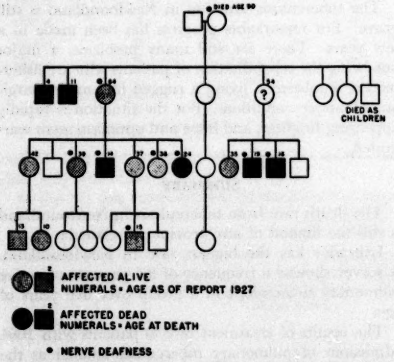

FIGURE 1. *Occurrence of Congenital Hereditary Hematuria in the Family Reported by Guthrie, Hurst and Alport.*

The fifty-four-year-old woman whose disease is questioned was thought to have the disorder by Guthrie[2] but not by the other investigators. Alport[4] reported nerve deafness in 2 of the 3 females he believed were unaffected in the first generation but did not specify which.

that the disorder was not as benign as he had thought. In some of the affected persons chronic nephritis had developed, and several had died in uremia.

Hurst and, particularly, Alport were impressed by the frequency of nerve deafness of varying severity in this family, occurring in members manifesting and those not manifesting hematuria.

In 1909 Aitken[6] described a family that seems to have suffered from congenital hematuria. No mention is made of deafness. It is of interest, in terms of genetic considerations, that the trait was transmitted not only by affected females but also by an unaffected male to all of his 6 children. Albuminuria, cylindruria and hematuria were found as early as the neonatal period.

Between 1875 and 1900 Dickinson,[7] Tyson,[8] Kidd,[9] Pel[10] and Eichhorst[11] described a high prevalence of chronic nephritis in 3 generations of the separate families reported by each. Others[12-19] have reported cases of familial nephritis. Whether all these are variants of the syndrome discussed by Guthrie is hard to tell.

Nerve deafness was also frequent in the family studied by Perkoff et al.[19] in 1951. This feature, coupled with the finding that progressive renal insufficiency developed only in males, links the syndrome he described with that of the earlier reports. However, the urinary findings in the patients of Perkoff and his associates were more suggestive of pyelonephritis than congenital hereditary hematuria or glomerulonephritis.

CURRENT CASES

During the past eighteen years we have cared for 8 cases of congenital familial hematuria occurring in 4 nonrelated families of Anglo-Saxon descent. Seven of these patients had albuminuria, hematuria and some cylindruria at all times although the hematuria varied from a few red cells in the centrifuged urinary sediment to bright-red urine. The eighth patient had intermittent albuminuria, hematuria and cylindruria; hematuria was never pronounced. Table 1 summarizes the age at discovery of the disease, present age and outcome; the different families are separated by the transverse lines.

TABLE 1. *Data in 4 Families Studied.*

PATIENT	SEX	AGE		KIDNEY FUNCTION	REMARKS
		WHEN SYNDROME DISCOVERED	AT PRESENT		
		yr.	yr.		
M.C.	F	5	24	Normal	
P.C.	F	5	14	Normal	
N.C.	F	4	13	Normal	Intermittent abnormal findings
C.C.	F	3	12	Normal	
R.S.	M	½	20	Normal	Nerve deafness
J.S.	M	1	17	Decreased	Nerve deafness
E.M.	M	7	9	Normal	Nerve deafness
R.M.	M	1	3	Normal	

Family Occurrence

M.C. is an only child. There is no known kidney disease in her family. P.C., N.C. and C.C. have no other siblings. Their mother has albuminuria and hypertension. R.S. and J. S. have 5 normal siblings. There is no known kidney disease in their family, nor does any other member of the family suffer from deafness. E.M. and R.M. are members of a family in which the frequency of kidney disease and nerve deafness is shown in Figure 2.

The disease in this family appears to have been more serious in the males, all but 1 of whom died in the teens or twenties. Post-mortem examinations disclosed small, shrunken kidneys. In the females the disorder has been compatible with a normal life span, 1 now being seventy-four years old. Most of them

have had albuminuria with minimal cylindruria and hematuria. During pregnancy there has been a tendency to hypertension, toxemia and edema. Deafness has been observed only in the patients who have the kidney disease as well. Some members of the family have congenital abnormalities of the eyes. The data in Figure 2 suggest that this syndrome is genetically a dominant.

Mode of Recognition

In the first patient, M.C., the disease was discovered when a routine urinalysis was done because of unexplained attacks of fever. The 3 sisters, P.C., N.C. and C.C., also had hematuria on routine urinalyses, after having had chicken pox. Both the brothers, R.S. and J.S., were found to have hematuria when they were admitted to a hospital for pneumonia and pneumonia with otitis media, respectively. When E.M. was admitted to this hospital for a tonsillectomy and adenoidectomy in the hope of improving the deafness, a preoperative urinalysis disclosed the urinary abnormalities. His brother, R.M., was brought to the hospital for confirmation of the diagnosis, which had been made by the mother.

Physical Examination

Except for nerve deafness in 3 of the boys, examination failed to reveal any abnormalities. The blood pressure was normal. All patients grew and matured normally.

Laboratory Data

Urine cultures and inoculations to guinea pigs for tuberculosis were negative. Kidney function, as measured by phenosulfonephthalein tests and urea clearance, was normal. Blood hemoglobin, nonprotein nitrogen and cholesterol concentrations were normal. The tourniquet test and bleeding, clotting and prothrombin times failed to show deviations from the normal. Intravenous and retrograde pyelograms were normal. A kidney biopsy was done on R.M. when he was two years old. Dr. Benjamin Castleman, chief of the Pathology Department of the Massachusetts General Hospital, gave the following report:

> There were a few undeveloped glomeruli, but the rest of the glomeruli were normal microscopically — no increased cellularity, no proliferation and no thickened basement membrane (PAS stain). The capillaries were wide open, and Bowman's spaces were clear. The convoluted tubules showed granularity of the epithelial cells, but this seemed to be consistent with secretory activity. A few of these tubules and many Henle loops were filled with fresh red blood cells. There was no necrosis of tubular epithelium. The interstitial tissue demonstrated little if any inflammatory reaction. The blood vessels appeared normal.
>
> The only abnormality was the blood in the tubules.
>
> Although glomerular disease could be fairly well excluded by this biopsy the sample was inadequate to rule out disease deep in the cortex medulla.

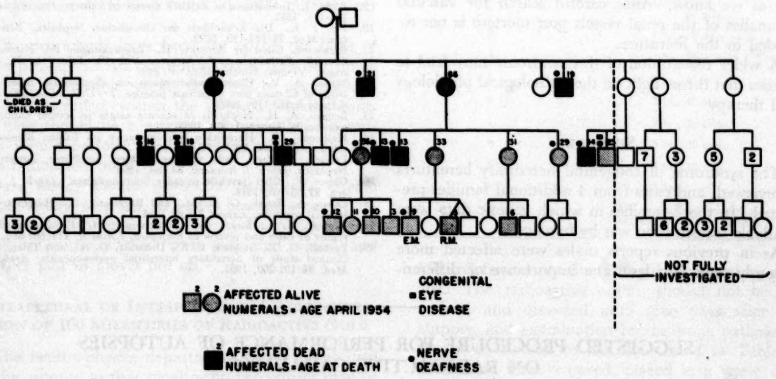

FIGURE 2. *Family Tree of E.M. and R.M.*
The numerals inside the patient symbols indicate the number of male and female children in the families.

Course

The course of the disorder in our 8 patients has been relatively benign. Exacerbations of hematuria are usually associated with infection of some kind but also occur spontaneously. In J.S. abdominal pain of such severity had accompanied exacerbations that he was admitted to the hospital 11 times for this complaint between 1946 and 1952. There have been no demonstrable signs of progressive kidney disease except in J.S., who at sixteen years of age manifested hypertension and a 25 per cent reduction of kidney function as measured by urea clearance.

However, the data presented in the literature as

well as the family history of E.M. and R.M. (Fig. 2) indicate that this syndrome may result in progressive renal disease.

There is no specific therapy known that modifies the hematuria or course of the disease.

No significant modification of the hematuria occurred during the administration of 20 mg. of cortisone to three-and-a-half-year-old R.M. daily over a four-month period. However, the dosage used and the repeated upper respiratory infections, in spite of prophylactic administration of penicillin, made this therapeutic trial inconclusive.

Studies of the permeability of glomerular capillaries by modern technics have not been reported as far as we know. Also, careful search for vascular anomalies of the renal vessels post mortem is not recorded in the literature.

A wider recognition of this syndrome may lead to studies that throw light on the pathological physiology and therapy.

Summary

The syndrome of congenital hereditary hematuria is reviewed, and cases from 4 additional families presented. In the 2 families in which genetic data were available transmission was by females.

As in previous reports males were affected more seriously than females. The importance of differentiating this syndrome from glomerulonephritis is emphasized.

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SUGGESTED PROCEDURE FOR PERFORMANCE OF AUTOPSIES ON RADIOACTIVE CADAVERS*

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BOSTON

THE increasing use of radioisotopes in medicine has resulted in many problems in protection of personnel associated with radioactive patients. An additional protection problem arises when a patient who has received a large internal therapeutic dose of radioisotope dies. If autopsy permission is granted, special procedures and precautions should be outlined for the pathologist. Recently (October 26, 1953) the National Bureau of Standards[1] issued recommendations in a handbook.

To provide a practical working procedure for this hospital the procedure described below has been established for the performance of autopsies on cadavers containing radiogold (Au-198). It is based largely on information about radiation exposure contained in the handbook referred to above.[1]

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This work was done under the United States Atomic Energy Commission Contract AT (30-1)-901 with the New England Deaconess Hospital.

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On the front of the chart of any patient receiving a therapeutic dose of radioactive gold is to be attached a hazard sheet indicating the isotope, the dose and date of administration. The admitting office is to be immediately notified after the administration of a therapeutic dose of radioactive material and will keep a record of all current hospital cases. All deaths in this group are to be immediately reported to the pathology department.

Radiogold is administered as a colloid and, hence, remains essentially where it is instilled. Radiogold has a half life of 2.7 days and emits beta particles having a maximum energy of 0.980 Mev and gamma rays having energies of 0.12 Mev and 0.41 Mev. The beta particles are attenuated by several millimeters of tissue so that they present no protection problem when the body is unopened. However, when the organs are exposed, the surface dose from the radioactive organs will be appreciable, and the handling time for these organs will need to be specified. The gamma rays associated with this isotope travel considerable distances through tissue and air; hence, protection pro-

cedures must also embody them. Fortunately, the intensity of gamma rays, like that of x-rays, from a small source of radiation varies inversely as the square of the distance from the source. For example, if one moves from a position of 30 cm. from a source to a position of 60 cm. from the source, the intensity of radiation at the 60-cm. distance is just a fourth of that at the 30-cm. distance.

There is a certain permissible dose of radiation[1,2] as recommended by the National Bureau of Standards. This rate is set at 0.300 r per week (300 mr) for whole-body exposure to x-rays or gamma radiation. For the hands and forearms the dose rate is set at 1500 mr per week, or, for a mixed exposure of betas and gammas, a millirep value of 1500 millirep per week.

The procedures have been set up on the basis of these principles. All procedures have been set up so that the permissible weekly dose will be approached, but not exceeded, within the allowed working time.

There should be a rotation of residents. No resident should perform weekly more than one autopsy on a radioactive body.

Bare hands should never be permitted. Gloves should always be worn. If gloves become torn or contaminated with gold they should be removed, the hands carefully washed with soap and water, and another pair of gloves put on.

Intrapleural or Intraperitoneal Administration of 100 Millicuries of Radioactive Gold

The health physics department should be notified of the autopsy so that monitoring procedures may be carried out at its discretion. If the autopsy occurs at a time beyond working hours, the health physics department should be notified at the beginning of the next working day.

For performance of the autopsy the following technic in the order presented should be followed:

In the first place fluid is aspirated from the chest or abdomen into a closed system. The collection bottle should previously have been labeled with the patient's name, the date, radioactive gold, a radioactive caution tag[3] and contents. The bottle should be set at a maximum distance from the working area and should not be disposed of until released by the health physics department. When the cavity is opened the remaining fluid is drawn up with a 180-cc. Asepto syringe, deposited in a properly labeled bottle and set at the same location as the first collecting bottle.

Secondly, by block dissection,[4] organs are removed from the contaminated cavity. One pathologist may spend four minutes working with his hands on the surface of the organs or cavity and ten minutes at a 10-cm. distance (or greater) from the cavity or organs.

No precautions except the wearing of rubber gloves are necessary if death occurs fifteen days after the administration of the active material.

The block dissection is placed in a previously labeled formalin-storage crock to which a radiation-warning sign[3] is attached, and then set aside for later examination. During the holding period the crock should be located at a distance not less than 150 cm. from a position normally occupied by anyone. The radioactive organs should not be examined and dissected until nine days after the autopsy, and examination by the same pathologist should be limited to the time listed in Table 1. Gloves are then removed, placed in a waste container labeled "radioactive gold" and held for the health physics department.

Table 1. *Handling-Time Chart.*

Death ____ Days after Administration of Au-198	Allowable Examination and Dissection Time 9 Days after Death
0	36 min.
1	45 min.
2	55 min.
3	1 hr., 8 min.
4	1 hr., 25 min.
5	1 hr., 45 min.
6	2 hr., 10 min.
7	2 hr., 40 min.
8	3 hr., 20 min.
9	4 hr., 10 min.
10	5 hr.
11	(No precautions except the wearing of rubber gloves)

Table 2. *Suggested Report of Radioactivity to Funeral Director.*

This certifies that the remains of _____ have been examined this date by the Radiation Safety Officer or his deputy.

Radioactivity at 50 cm. from the surface of the body, as determined by _____ is below the rate of 50 mr. per hour. If the body is embalmed by injection procedures, the above rate will not present any hazard provided not more than six hours a week are spent in embalming such bodies.

Rubber gloves must be worn during the embalming, and further precautions taken as listed below.

Further precautions _____

_____

_____

_____

Signed _____
Radiation Safety Officer

Thirdly, another pair of surgical gloves is worn for the rest of the autopsy.

Finally, when the body is surrendered to the undertaker, a radioactive form such as that presented in Table 2 should accompany it.

If a dose of 200 millicuries was administered, all

handling or working times presented must be halved; it may be necessary to have a relay of pathologists to perform the autopsy.

Intrapleural or Intraperitoneal Administration Without Autopsy

If death occurs within six days of administration of radiogold the body should be taken to the morgue, where the ascitic or pleural fluid* should be withdrawn by a pathologist into a closed system, set at a maximum distance from working areas and held until released for disposal by the health physics department. When the body is surrendered to the funeral director a radioactivity form (Table 2) should accompany it.

If death occurs six days after administration of radiogold, no aspiration is necessary, but a radioactivity form should be given to the funeral director.

*Withdrawal of the fluid that contains some radioactivity would minimize the radiation exposure to the embalmer.

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MEDICAL PROGRESS

PERIPHERAL VASCULAR DISEASES*

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BOSTON

Since 1949, when the last progress report was published,[82] important advances have been made in the surgical treatment of peripheral vascular diseases, especially in the replacement of injured and diseased arteries by some type of blood-vessel graft. This does not mean that sympathetic neurectomy and other methods in use for many years have been supplanted, but that the restoration of continuity of a major artery with vascular grafts is a supplement to the older and more established procedures.

Diseases of Arteries

Peripheral Arteriosclerosis

The problem of arteriosclerosis is an ever-growing one because of the increasing longevity of the general population. Manifestations of this degenerative disease are becoming more common, and newer methods of therapy are being devised for more adequate treatment.

A better understanding of the pathogenesis of this disease is important, and this goal is slowly being attained. Duguid,[14] who advanced an interesting concept regarding the cause of arteriosclerosis, demonstrated that mural thrombi of fibrin, which produce partial occlusion of the lumen, become covered with endothelium and gradually flatten out to give the picture of sclerosis. By injecting fragments of fibrin clot into a rabbit's vein he created a microscopical picture of atherosclerosis in the pulmonary arteries. He points out that anything within an artery, even a thread, quickly becomes subendothelial by overgrowth of endothelium.

Wessler et al.,[50,51] in extensive radiologic studies of calcification in arteries of the lower extremities, emphasize the fact that the demonstration of this calcification does not necessarily bear any relation to the presence or location of arterial occlusion. These findings are corroborated by the work of Lindbom[31] and Silbert, Lippman and Gordon.[43]

Tobacco appears to be a contributing factor in the production of arteriosclerosis. Barach[1] states that there is overwhelming prevalence of arteriosclerosis in persons who use nicotine. Dologoff and his associates[12] estimated that the relative frequency of coronary-artery disease in heavy cigarette smokers was one and a half times that in nonsmokers. Roth[40] demonstrated, by plethysmography and skin-temperature studies, that smoking or hypodermic nicotine administration produced vasoconstriction. According to Winsor[58] the vasoconstrictive effects of smoking are related to the amount of nicotine inhaled.

Methods of study. Digital plethysmography is being employed as a laboratory method of evaluating the arterial circulation of an extremity under certain conditions.[52] Other laboratory procedures useful in investigating peripheral arterial disease under varying environmental circumstances include measurement of skin temperatures, arterial pulsations, walking ability, muscular endurance (ergometry) and sweating activity.[8] A new, versatile, direct-writing electroplethysmograph has been introduced.[44] Buchanan et al.,[6] utilizing digital plethysmography and skin-temperature recordings, have demonstrated in a semiquantitative way the local vasoconstricting effect of exposure to cold in sympathectomized extremities.

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The introduction of radiographic technic for the visualization of arterial pathways, by the intraluminal injection of opaque substances, has opened a new vista for direct surgery of arteriosclerosis.[18,45] Aortography was originated by dos Santos.[13] Leriche,[29] who was an early advocate of the method, has presented a collection of twenty-two full-page, selected x-ray photographs of aortograms based on a series of 100 cases. An interesting study of post-mortem arteriograms in so-called normal limbs by Ross and Keele[39] revealed that in 7 of 100 lower extremities occlusive changes were surprisingly great; in none of these patients had there been any complaint of symptoms suggesting vascular insufficiency because of the adequate collateral circulation present.

Deterling,[11] discussing direct and retrograde aortography, reports that in more than 95 patients on whom the technic was used there were 2 cases of transient encephalopathy and 3 of chemical neuritis. All patients received 80 per cent sodium iodide. The author adds that retrograde abdominal aortography appears to have no advantages over the translumbar route, and that there are definite practical disadvantages. In the thoracic aorta the direct approach has been less successful than the retrograde method, though a poor visualization and 1 related death in 3 patients followed injection via a catheter through an ulnar artery into the thoracic aorta. Excellent visualization but 2 serious complications resulted from the introduction of a catheter into the left common carotid artery of 12 patients.

Leriche and his associates[30] later reported their experience in the interpretation and value of aortography in 200 patients. The indications were obliterative arteritis with absent femoral pulses, aneurysm, arteriovenous fistula, aortic embolism, patients expecting rectal surgery who are known to have obstructive peripheral vascular disease, abdominal masses, suspected renal or suprarenal tumors and suspected placenta praevia. The contraindications were poor renal function, allergy to iodine, extremely poor general condition and impending gangrene of the extremity. It was believed that the spasm produced by aortography could precipitate gangrene. The complications listed were minimal discomfort, iodine sensitivity, air in the aorta, temporary hypertension and extravasation of dye. The last unfortunate circumstance, although not dangerous, is very painful up to twenty-four hours. Saline solution and novocain should be injected into the region.

Freeman and his colleagues[20] recommend the Valsalva maneuver as an aid to contrast visualization of the aorta and great vessels. Temporary diminution of the cardiac output by means of a forced expiratory effort against the closed glottis results in a high local concentration of the dye in the slowly moving blood stream. This technic was used in 13 patients, with successful visualization in 10. Regarding the actions of intra-arterial injections of Diodrast, Thorotrast and sodium iodide on the peripheral pulse volume of the lower extremity, Jepson and Simeone,[25] in a plethysmographic study on 3 patients after a similar investigation on 9 dogs, concluded that the vasoconstriction resulting from the injection of Diodrast is insufficient to explain the occasional femoral-artery thrombosis reported in the literature. It was suggested that internal trauma and traumatic arteriospasm, especially in the diseased artery, are more likely explanations. In a series of 50 abdominal arteriographies Wagner and Price[48] report a fatal outcome that probably resulted from mesenteric thrombosis. The needle accidentally entered the orifice of the superior mesenteric artery, which received the 80 per cent sodium iodide solution intended for the abdominal aorta. These authors recommend a preliminary injection of a dilute solution to ascertain the whereabouts of the needle. They add that dos Santos has done over 300 injections without a single accident, that Osario has performed 100 without accident and that Nelson has reported over 100 procedures without a death.

Methods of treatment. Lumbar sympathectomy continues to be a mainstay in the treatment of arterial insufficiency of the lower extremities.[16] Anatomic studies in relation to surgical significance have been presented by Lowenberg and Morton[33] and by Edwards.[15] Blain and Campbell[6] conclude that sympathectomy is a very effective procedure in the treatment of selected cases of arteriosclerosis of the lower extremities. They also stress the importance of the operation on an unamputated side in unilateral amputees, for the remaining limb must thereafter do twice the work. Coller et al.[9] review the early results of lumbar sympathectomy for arteriosclerotic peripheral vascular disease. Their series includes 74 operations on 63 patients, most of whom were in the sixth and seventh decades of life. Symptomatic improvement in pain, coldness and claudication was obtained in approximately 80 per cent of the group. The value of lumbar sympathectomy in arteriosclerotic gangrene was pointed out by Gerber and his associates.[24] In 19 patients with late peripheral arteriosclerosis and necrotic phenomena treated by removal of the second and third lumbar ganglions improvement and healing took place in 14. The remaining 5 required amputations. Nine of the entire group were diabetic, but there seemed to be no specific relation between the result obtained and the presence or absence of diabetes. DeBakey, Creech and Woodhall,[10] in a series of 146 consecutive patients who underwent lumbar sympathectomy for arteriosclerotic peripheral vascular disease, also observed no essential difference between the diabetic and nondiabetic groups except in those with frank gangrene, in whom a somewhat higher incidence of improvement was observed among the diabetic patients. Kirtley, Garrett and Martin[28] reported that all 78 patients operated on for vasospastic disorders, 82 per cent of 22 victims of thromboangiitis obliterans and 76 per cent of 100 patients with periph-

eral arteriosclerosis were improved. Criteria for obtaining better selection in the last group were suggested. These authors recommended the early use of heparin therapy in selected cases with impending gangrene to forestall the paradoxical gangrene. An explanation for this complication, which occurs in a previously sympathectomized extremity during the performance of the procedure on the opposite side, is offered by Felder et al.,[19] who propose a supersensitivity of the denervated peripheral sympathetic ganglions and end organs to either asphyxia or epinephrine. They reached these conclusions after observing the fall in skin temperature of previously sympathectomized limbs during ether anesthesia. This drop did not occur with spinal anesthesia.

In view of these studies it is recommended, in a bilateral, two-stage lumbar sympathectomy, that the second side be done under some other anesthetic agent, such as spinal, rather than ether. Thompson, Brose and Smithwick[47] point out, in studying patterns of electric skin resistance in 177 patients after sympathectomy, that the major pathways of sudomotor outflow to the lower extremities come from the first and second lumbar ganglions.

Leriche and his school have maintained that the presence of a segment of thrombosis in an artery sets up reflex vasoconstriction, on the basis of a special irritative condition in the wall of the involved vessel. This irritative condition, according to Bernhard,[4] can lead simultaneously to vasoconstriction of the opposite limb and to disturbances in the entire vegetative nervous system. This author reports 8 cases of resection of the area of occlusion in the femoral arteries, with a successful operation in all. He states that arterial resection is justified in the presence of ulcer formation or threatened gangrene. Mentha[35] performed 94 arteriectomies in 80 patients, the oldest of whom was seventy-five years of age. In 45 patients an associated sympathectomy was done. In those who underwent arteriectomy alone the results showed an improvement in 45.7 per cent, no change in 22.8 per cent and failure in 25.7 per cent; 5.7 per cent of this group died. Freeman and his associates[21] reported 9 cases of arteriectomy for intractable pain after recovery from acute arterial occlusion. The limbs were viable, but intractable pain, relieved by sympathetic block, had developed. Two patients died postoperatively of coronary occlusion. Arteriectomy, the authors state, is a relatively minor procedure, and can be done even in the poor-risk patient. Local anesthesia is employed, and usually only 2 or 3 cm. of the thrombosed vessel is excised. They believe that the relief of pain is the result not of any improvement in circulation but of interruption of some nerve reflex from the region of the thrombosed artery.

Insidious thrombosis of the aorta, with a report on 10 cases, is discussed by Elkin and Cooper.[17] The surgical procedures recommended are bilateral lumbar sympathectomy or resection of the aortic bifurcation. Ortner and Griswold[36] report 3 cases of chronic occlusion of the bifurcation of the aorta in which both resection of the thrombosed segment and bilateral lumbar sympathectomy were carried out; these authors believe that the sympathectomies alone were sufficient. Sautot[41] describes 2 cases of aortic thrombosis treated by resection, adding that when resection cannot be done lumbar sympathectomy is the only therapy available. Oudot and Beaconsfield[37] successfully treated 5 patients with thrombosis of the aortic bifurcation by resection and homograft replacement. Beaconsfield and Kunlin[3] report 35 cases of this condition. In a discussion of the thrombosis of the terminal aorta, Theis[46] states that bilateral lumbar sympathectomy will improve the peripheral circulation and that resection of the terminal aorta is not advisable. The extent of the disease and the remaining artery makes closure of the lumen difficult, and both collateral vessels and channels through the thrombus would be removed with the resection. Burt, Learmonth and Richards[7] have reported 11 patients with aortic thrombosis in whom high bilateral lumbar sympathectomies were performed.

Blood-vessel grafts — either homologous, arterial or venous or autogenous ones—have been widely used during the past few years. The method is of value especially in the presence of short segmental areas of occlusion in the superficial femoral artery to relieve intermittent claudication and to save some extremities that otherwise would require amputation because of ischemic lesions of the feet and lower leg.

A series of 19 venous grafts were placed in the superficial femoral arteries of 18 patients by Julian and his co-workers,[26] with restoration of pulses and relief of claudication in 12. Seven cases were failures. Of the entire group 3 were saphenous-vein homografts, 14 were saphenous-vein autografts, and 2 were superficial-femoral-artery autografts. Julian et al.[27] subsequently reported placement of autogenous saphenous-vein grafts in 34 cases, with 12 failures. The longest graft was 32 cm. in length. Four homologous saphenous-vein grafts implanted on the same day that they were obtained, and hence not considered preserved, were employed, with no failures in the group. Rob[38] employed frozen homologous arterial grafts to replace segments of femoral artery in 25 patients with 2 thromboses; he used vein grafts in 5 cases, with 3 thromboses. Schmitz and his associates,[42] in a series of venous autografts implanted into the abdominal aortas of growing pigs, found that delayed thrombosis was frequent when the graft diameters were larger or smaller than that of the host vessel, or when the grafts were made isodimensional by plication. In summary it can be stated that grafts are of undoubted value in the treatment of obliterative diseases of major arteries. As yet the supply of satisfactory grafts is limited, but this difficulty will unquestionably be solved soon.

Thromboendarteriectomy of various portions of the

aorta and iliac and femoral vessels was performed by Wylie et al.[54] on 12 patients, with no operative deaths but with two later deaths from cerebrovascular accidents. Thrombosed segments varied from 7 to 22 cm. in length. These patients required amputation. In 4 cases it was necessary to construct additional support from a fascia-lata graft.

In a later publication Wylie[55] reported a series of 26 thromboendarteriectomies, with restoration or improvement of the peripheral arterial circulation in 19 patients; length of resected specimens varied from 12 to 52 cm. Barker and Cannon[2] performed endarteriectomies on 18 patients with chronic obstruction of major arteries. Seven amputations were necessary, and 2 of the patients died. Specimens resected varied from 5 to 60 cm. in length.

Regional injection of heparin by means of a needle or polyethylene catheter into the artery proximal to the suture line was carried out in a series of 5 patients by Freeman and his associates,[22] after removal of emboli and after arterial repair that followed an injury or excision of an aneurysm. They stated that this form of administration was of value in preventing thrombosis at the suture line and that the danger of hemorrhage from the wound was decreased. In a subsequent article Freeman and Gilfillan[23] presented their experiences with regional injection of heparin after thromboendarteriectomy in 12 cases. In 6 patients restoration of the lumen of the obstructed artery was clearly demonstrated. Generalized anticoagulant therapy with Dicumarol was employed postoperatively, and hemorrhage was not a complicating factor in any of these patients.

The value of transmetatarsal amputation has been graphically demonstrated by McKittrick et al.[34] Two hundred and fifteen of these procedures were performed from 1944 to 1949 for infection and gangrene in patients with diabetes mellitus, the results being completely satisfactory in 135 of the cases. In 32 patients the end result was still undetermined at the time of publication and was regarded as unsatisfactory. Amputation at a higher level was necessary in 7 cases after complete healing for a minimum of a year. The functional result was excellent in all successful cases. Warren and his associates[49] more recently reported their experience with 43 transmetatarsal amputations for arterial deficiency of the lower extremity. In 62.8 per cent of the patients the wounds healed, and the limbs were useful.

Thromboangiitis Obliterans

A re-evaluation of the clinical entity known as thromboangiitis obliterans is probably needed because of knowledge that is being gathered regarding the pathology of arterial disease in young patients with obliterative arterial disease by means of arteriography. Many persons with previous diagnoses of Buerger's disease are actually suffering from peripheral arteriosclerosis. In women this disease is rare,[57,59] only a few cases having been substantiated in the literature. Superficial migratory phlebitis is still considered an aid in diagnosis but is not essential, nor is it always present. Smoking should without a doubt be completely discontinued by these patients, and occasionally the progress of the disease is arrested with this measure alone. Eisen et al.[58] report that discontinuation of smoking, in active thromboangiitis obliterans, causes a drop in platelet adhesiveness. Lumbar sympathectomy, however, is still the most effective therapeutic measure available,[56,60,61] but must be supported by the cessation of smoking.

Vascular Transplants

The surgery of major blood vessels has made rapid strides in recent years, especially regarding the insertion of venous or arterial grafts for diseased or injured arterial segments. The horizon of this particular aspect of vascular surgery, however, continues to broaden.[84,85,88,89,96,98]

Cooke et al[64] reported on the use of grafts to repair traumatic arterial defects. Dickinson, Ashley and Gerbode[67] discussed grafting procedures, along with other methods of repair of vascular injuries, as employed during the Korean War. In a consideration of major vascular injuries in battle casualties, Jahnke and his associates[73,74] stated that the therapy of choice was primary repair by direct end-to-end anastomosis or by autogenous venous grafts. Swan and Morfit[98] used preserved grafts in the treatment of neoplastic disease involving peripheral arteries. Macpherson and his coworkers[82] successfully employed venous homografts to repair experimental aortic defects. Freeman and Leeds[68] used vein inlay grafts in the treatment of aneurysms and thrombosis of the abdominal aorta. Johnson et al.[75] placed venous grafts between the subclavian and pulmonary arteries in 2 patients with tetralogy of Fallot. Conley[63] reported on the use of free autogenous vein grafts to the internal and common carotid arteries in the treatment of tumors of the neck in eleven patients. Gross[70] employed homologous grafts in repairing coarctation of the aorta and in congenital heart disease, with excellent results. Hurwitt and Kantrowitz[72] fabricated grafts from segments of the splenic artery, which were successfully implanted in the aortas of laboratory animals. Potts, Albert and Fischer[90] used segments of the femoral artery in the same manner.

Storage of arterial and venous grafts may be done by any of several satisfactory methods. Which of these is the most effective and practical is yet to be learned. Meeker and Gross,[83] in 1951, described a method of sterilization of blood-vessel grafts by high-voltage cathode-ray irradiation, the grafts then being stored in sealed containers in carbon dioxide ice at −60°C. In this manner blood vessels may be removed without aseptic technic and also from patients who may have died from infections of neoplastic diseases. This method has proved satisfactory in our hands at the Massa-

chusetts General Hospital during the past year.[93] Deterling et al.[65,66] employed quick freezing at −72°C. in carbon dioxide ice and 95 per cent alcohol mixture and storage at very low temperatures (below −60°C.) in an insulated box containing solid carbon dioxide ice. Coleman, Deterling and Parshley[62] suggested using grafts preserved in nutrient mediums at 4°C. when periods of storage were anticipated to be six weeks or less; otherwise, freezing, as mentioned above, was recommended.

Swan and his associates[97] prefer rapid freezing at −78°C. in nutrient mediums and storage at this temperature. Gross et al.[69] employed vessels stored at 1 to 4°C. in repairing coarctations of the aorta in human beings but warned that the upper limits of safety for this method of storing were thirty-five to forty days, based on tissue-culture studies of viability and results obtained after the use of these grafts in laboratory animals. Hufnagel and Eastcott[71] recommend quick freezing to minimize crystallization and storage in a solid carbon dioxide bank rather than a deep-freeze appliance. Encouraging results with lyophilization, or freeze drying,[66] are being obtained in several medical centers, but methods and results of this technic have not found their way as yet into the general literature.

It is now generally accepted that no portion of the homologous graft remains viable but that it simply forms a temporary conduit until the host, using the graft's elastic tissue[94,96] as a scaffold, can replace its structure with host tissue. According to Swan[94,96] all cellular elements are destroyed by the host at the end of the third week. Elastic tissue, however, persists for at least two years. In about a month a firm, fibrous-tissue outer layer has been formed around the graft, and a new inner layer grows in from each end of the graft. The host tissue is at first fibrocellular but later undergoes remarkable differentiation. The inner cells assume endothelial forms, and new elastic fibrils are laid down.

McCune and his colleagues[81] have studied the nutrition of transplanted arterial homografts by India-ink injections into the vessel lumens and into the general circulation, and by wrapping the grafts in cellophane. They concluded that practically all the circulation reaching the graft walls is derived from surrounding structures and to a small extent from the anastomosis at the graft ends. No vessels could be demonstrated entering the graft walls from the lumens. Nevertheless, in cellophane-wrapped grafts the histologic appearance of the layers immediately surrounding the lumen was more normal than that of the outer media and adventitia, indicating presumably that some nutrition filters through the endothelium from the lumen to supply the internal and inner medial coats. The authors therefore recommend that grafts, when used, be surrounded by as much vascular tissue as possible to promote vascularization.

Peirce[87,88] states that thrombosis and disruptions of arterial grafts, when they occur, do so within a brief danger period after implantation, and that these absolute failures are more frequent when nonviable tissue is employed. Swan et al.,[94] on the other hand, using canine aortic homografts, state that the duration of storage does not appear to be a significant factor in the immediate functional success of the transplant. Sauvage and Harkins,[91,92] employing aortic and vena-cava homografts in the growing pig, concluded that the duration of the period of preservation before implantation does not significantly influence either the incidence of thrombosis or the pattern of the dimensional changes of the graft with growth of the pig. Johnson and his associates,[77,79] however, after concluding by pig experiments that autogenous vena-cava and aortic grafts do not limit growth (at least not rapid growth), questioned whether these results are applicable to children, in whom slower growth might provide time for the development of mature connective tissue that might limit growth. Homografts studied in the same fashion[78] did show limitation of growth. The same authors pointed out, in experiments on young pigs, that the use of continuous posterior and interrupted anterior silk sutures, in simple blood-vessel anastomoses (not employing grafts) does not significantly limit the growth.[76] McCune and Blades[80] report that the length of transplants has no effect on the viability. None of the 11 longest vessels (18 to 22 cm.) used by them manifested thrombosis.

It is too early to tell which type of grafts will stand the test of time without degenerative changes that may lead to obliteration or aneurysmal dilatation. From the theoretical point of view it seems that the autogenous grafts would be the most likely to survive without serious change, since they remain as living tissue with some elastic and muscular tissue, whereas the homologous grafts are replaced by the host's connective tissue. It is essential, therefore, that careful follow-up studies be made of all types of grafts since it may require ten or more years to clarify this matter.

Therapeutic Venous Occlusion

On the question of concomitant venous ligation in acute arterial occlusion, Cullen and his associates,[99] on the basis of extensive experimental evidence in laboratory animals, conclude that no benefit accrues from this procedure. Simeone, Grillo and Rundle[102] state that ligation of the concomitant vein causes no improvement in muscle function. Experiments utilizing the gastrocnemius-soleus group of muscles in the cat were performed. The acute effects of venous occlusion on the rate of arterial inflow to the hind limbs of cats have been studied directly, by perfusion and by serial radiography, by Thompson and Vane.[103] Concomitant clamping of the accompanying vein, they conclude, fails to cause an increase in arterial blood flow to the limb when the major artery has been clamped. Shepherd,[101] using a mechanical compres-

sor over the femoral artery and vein, together with venous occlusion plethysmography of the calf, obtained results suggesting that concomitant venous occlusion has a detrimental effect on the collateral circulation of the limb.

Despite these reports of the ineffectiveness or even detrimental effects of therapeutic venous occlusion, it must be pointed out that intermittent venous occlusion, when properly administered, can be used to save ischemic limbs after major arterial occlusion, when other methods such as vascular grafts are not possible.[100]

Raynaud's Disease

Sir Thomas Lewis maintained that Raynaud's disease was due to an increased sensitivity of peripheral vessels to cold. Later investigators postulated a hyperreactivity of the sympathetic system or a combination of both mechanisms.[104] It is certain, nevertheless, that recurrences of vasospasm frequently follow an inadequate dorsal sympathectomy. These recurrences could be due to regeneration of the sympathetic fibers or to a readjustment along residual pathways, if hyperreactivity of the sympathetic system was the etiology of the disease. If a local fault was the explanation a persistence of the abnormality would explain recurrences of the condition. Though both explanations probably contribute more or less to the reappearance of symptoms, local vessel sensitivity to cold may be a predominant etiologic factor and consequently a principal reason for the perseverance of vascular spasm. This opinion is based on experimental evidence obtained in the Peripheral Vascular Laboratory at the Massachusetts General Hospital, where it has been shown in several cases of Raynaud's disease that the critical temperature producing arteriolar spasm in each patient was not significantly lowered by sympathetic block or sympathectomy. The method consisted of digital plethysmography and skin-temperature recordings taken during immersion of the hand in a water bath of regulated temperature. It should be emphasized that these experiments do not indicate that sympathectomy is not beneficial. On the contrary, when the patient's peripheral vessels are constantly maximally dilated and heated by the warm blood coursing through them, falling of the vessel temperature to the critical level is not as easily produced; also, cooling of these vessels by vasoconstriction can no longer be brought about reflexly from emotions, pain or body chilling.

A radical sympathectomy to include the inferior cervical and the first three dorsal ganglions and also the second and third spinal nerves within their roots is recommended to assure removal of the efferent pathways and to reduce the facility of regeneration to a minimum. Although the chief outflow of the upper extremity is through the second and third intercostal nerves by way of the second and third ganglions there is, in many patients, an outflow through the first dorsal nerve directly to the first dorsal ganglion and possibly the inferior cervical ganglions. To be adequate, therefore, the operation must produce a Horner syndrome. For lower extremities afflicted with this malady the problem is not as complex, and clinical improvement follows lumbar sympathectomy in almost all cases. Results of treatment by sympathectomy have been reviewed by Felder et al.,[105] Jepson[106] and Robertson and Smithwick.[107]

Vascular Spasm

Several interesting publications on the subject of vascular spasm have recently appeared.

Martin, Laufman and Tuell,[110] observing micrometric patterns of response in small mesenteric vessels of young dogs after acute *venous* occlusion, report that in the control group, after occlusion of the mainstem vein, the artery goes into reflex spasm whereas the vein becomes moderately dilated. On release of the occlusion there is a period of residual spasm in the artery while the vein returns to preocclusion caliber. After sympathectomy, however, all reflex arterial spasm, as well as the residual arterial spasm that follows release of the occlusion, is abolished. The vein becomes dilated to a diameter exceeding that of the control during occlusion. One hundred per cent oxygen has no effect on the pattern of vasospasm in venous occlusion. Papaverine given during reflex arterial spasm abolishes some of the spasm. After release of the occlusion there is no phase of residual spasm.

After acute *arterial* occlusion in the same type of experiments the authors report that in the control group the artery goes into severe spasm whereas the vein exhibits a mild degree of spasm. On release of the occlusion there is a period of residual spasm in the artery and a similar period in the vein. Sympathectomy abolishes all spasm in both artery and vein, during occlusion as well as after release. In some cases reactive hyperemia is reflected in the caliber of the small artery after release of the occlusion. One hundred per cent oxygen has no effect on the pattern of vasospasm in arterial occlusion. Papaverine given during arterial occlusion has no effect on arterial spasm but, after release of the occlusion, abolishes residual spasm.

Kinmonth, Simeone and Perlow,[108] in experiments on laboratory animals, have discussed factors affecting the diameter of large arteries, with particular reference to traumatic spasm. The results suggest that although the femoral artery is not under direct control of the nervous system (sympathetic or systemic), it can alter its size on a myogenic (stretch) basis, and also as a passive reflection of systemic blood pressure. Local segmental spasm in the large arteries can be produced by mechanical trauma irrespective of the presence of the adventitia and possible nerve supply. Direct electric stimulation, however, produces no change.

Kinmonth[109] employed the following drugs to relieve traumatic arterial spasm: papaverine, procaine, caffeine, Priscol, heparin and benzodioxane. The best results were obtained with papaverine, which consistently produced relaxation a few minutes after the artery was covered with a 2.5 per cent solution.

Pickering,[111] however, warns that at present the idea that vascular spasm causes the manifestations of disease is entertained too freely and too uncritically. He emphasizes the fact that organic vascular narrowing or occlusion may mimic vascular spasm, and that true spasm is a rare, rather than a common, condition.

Causalgia

A series of 142 soldiers suffering from post-traumatic vasomotor disorders is reported by Shumacker and Abramson,[113] with particular reference to late manifestations and treatment. For the acute stage of pain, swelling, coldness, hyperhidrosis and cyanosis, the authors recommend débridement (removal of foreign bodies, setting of fracture and so forth) and early mobilization if possible. Also advised are correction of psychiatric ailments and avoidance of chronic invalidism. If sympathetic blocks have a good effect, sympathectomy may result in cure.

For treatment of the later stage of pain on exercise and weight bearing, cold sensitivity, coldness, hyperhidrosis, cyanosis and even ulceration the authors recommend psychotherapy, exercise, the avoidance of edema by elevation and sympathectomy, if sympathetic blocks are helpful.

According to Kuntz,[112] some afferent spinal nerve fibers reach the extremities through the sympathetic trunk. This was demonstrated by histologic study of osmic acid preparations of gray communicating fibers or sympathetic roots, which join the brachial and lumbosacral plexuses in man, and corresponding rami in cats. Stimulation of appropriate sympathetic nerves in man and animals showed conduction of pain impulses by these afferent fibers, which appear to be distributed chiefly in relation to the blood vessels rather than to the skin and muscles of an extremity. It is postulated that they play a significant role in mediation of deep pain in the extremities, particularly pain of vascular origin. Certain patients with phantom pain after amputation or special types in paralyzed extremities, this author states, have alleviation of pain after extirpation of the lumbar sympathetic chain. These afferent fibers, which reach the extremity through the sympathetic trunk, are said to conduct not only impulses that result in painful sensation but also impulses that reflexly activate the patent sympathetic nerves in the extremity. Such reflex stimulation tends to increase vasomotor tonus in the extremity and to aggravate the pain. In these patients interruption of the sympathetic nerves is recommended for alleviation of pain by eliminating an important afferent pain pathway and by abolishing vasomotor tonus.

Frostbite

There has been a reawakening of interest in the study of frostbite and related cold injuries because of the large number of these casualties sustained during the recent Korean conflict.[115] Lempke and Shumacker[117] and Shumacker and his associates[119,120] have carried out a series of controlled experimental investigations, which reveal that immediate, rapid thawing is the most effective single therapeutic measure in preventing subsequent gangrene. Intensive anticoagulant therapy[122] is also of benefit. The place of sympathectomy, however, has not been as definitely established. Arena et al.,[114] in animal experiments, conclude that early release of vasospasm by administration of tetraethyl ammonium chloride during the acute stage of frostbite causes increased edema and a transient, wet type of gangrene to replace the dry gangrene seen in control animals. However, in the intermediate and late treatment of frostbite, according to Shumacker[121] and Isaacson and Harrell,[116] the indication for sympathectomy is certain. ACTH apparently has no effect.[118]

Embolism

Little advance has been made in the treatment of this condition except that immediate embolectomy is recognized by more and more doctors as the best therapeutic measure in the majority of patients. The ideal treatment to restore circulation in a limb after embolization is to remove the embolus as soon as possible to prevent distal thrombosis from occurring. Even after removal of the embolus and as much of the distal extension as possible the circulation will not be restored because the thrombi cannot be removed from the smaller arteries of the limb.[126,127,186] Spasm of the arterial tree distal to the site of embolization contributes greatly to stagnation of the flow and subsequent thrombosis. Six hours[123] has been recommended as the golden period within which the best results, statistically, have been obtained. In limbs surviving with conservative treatment or with embolectomy many hours after initial lodgment, it can be assumed that distal extension of the clot progressed as far as a fair-sized collateral branch and that the rate of flow through this branch discouraged propagation of the clot beyond this point.

Linton,[131] in a report discussing the technic for removal of a saddle embolus at the bifurcation of the aorta, stresses the importance of six principles: early operation; direct and adequate exposure of the site of embolism; occlusion of the artery distal to the embolus before the artery is disturbed, at or proximal to the site of embolism; avoidance of damage to the intima; and complete control of the arterial inflow both proximal and distal to the arteriotomy, so that a meticulous intima-to-intima closure was accomplished.

Albright and Leonard[123] add 3 cases of saddle embolism at the aortic bifurcation to the 190 cases re-

ported in the literature up to that time. In reviewing the statistics they state that of the 193 patients described in the literature, 144 died as a result of the embolism, 26 were cured by direct or indirect embolectomy, 8 recovered by conservative measures, 11 survived after amputation, and 4 recovered with no treatment.

Tropea and Entine[138] report the forty-second successful embolectomy from the aortic bifurcation.

Because rheumatic mitral disease is a well known cause of recurrent embolization resection[124] of the left atrial appendage has been recommended for this condition. Baronofsky,[125] however, prefers ligation of the appendage because of the simplicity of the procedure as compared to resection. Three cases with satisfactory results during postoperative convalescent periods are reported. In the performance of 901 mitral-valve operations Bailey, Glover and O'Neil, according to Tropea and Entine,[138] produced a total of 28 emboli, 9 of which were peripheral, the remainder being cerebral. Lord and Burke[133] state that the treatment of aortic saddle emboli includes prompt embolectomy, long-term anticoagulant therapy and resection of the left atrial appendage, with mitral comissurotomy when indicated. Leonard and Cogan,[130] in discussing the failure of ligation of the left atrial appendage in the prevention of recurrent embolism, state that only 23 per cent of emboli originate solely from the appendage. These authors recommend the use of Dicumarol.

In a study of 330 unselected cases of embolism of the extremities, Haimovici[128] observes that the source of the emboli was the left side of the heart in 96 per cent of the cases.

Andrus,[124] in evaluating conservative treatment in 75 cases of peripheral arterial embolism in 65 patients, found that in 10 patients with saddle emboli there were 7 deaths. Only 2 patients of the 10 were operated on; 1 survived, and 1 died. Of 5 patients with iliac embolism, 4 died. In 50 patients with limb emboli there were 16 deaths.

Veal and Dugan[139] suggest the following plan in the treatment of peripheral arterial embolism. In the first place a sympathetic nerve block is performed, and the operating room prepared for surgery. If, in thirty minutes, the full effect of the block is noted conservative therapy is continued. If there is no effect from the nerve block the embolectomy is performed. Secondly, after either of the above courses has begun, anticoagulants are given.[138] Of 28 patients treated by the authors (all before eight hours), 16 required embolectomy, and 12 responded to conservative treatment. Embolectomy failed in 3 cases. Holden[129] reports a series of 14 cases of embolism of the common femoral artery seen within ten hours. Embolectomy was performed in 8 patients, all of whom recovered. Of the 6 patients treated conservatively 2 died, 3 required amputation, and 1 had evidence of postembolic ischemia. Martin, Laufman and Tuell[135] warn that too zealous performance of sympathectomy for acute arterial occlusion may endanger survival of precarious limbs by temporary reduction in blood pressure after operation.

Olwin, Dye and Julian,[137] discussing late peripheral arterial embolectomy, describe 6 patients operated on twenty-two hours, four days, six days, three months and three and a half months after embolism. In 4 patients function was restored to normal or near normal. The fifth patient died of uremia, possibly secondary to restoration of blood flow to a questionably viable limb. In the sixth patient further thromboses interfered with normal restoration, but material improvement was noted.

Aneurysms

Aneurysms of major arteries have presented a challenge to surgeons throughout the ages. Only in relatively recent years have satisfactory methods of therapy for this condition evolved.

Treatment of aortic aneurysms by wrapping with impure polythene film in 9 patients was reported by Poppe,[147] with survival of 4 of the patients for one to three years. In 1 patient autopsy one and a half years later showed fibrosis on both sides of the film. Grindlay and Waugh[149] placed a thin sheet of polyvinyl sponge over the wall of large abdominal aneurysms in 4 patients with the expectation that fibrous tissue growing into the sponge would strengthen the aneurysm. Wilkinson[150] treated an aneurysm of the abdominal aorta in a sixty-seven-year-old man by placing a layer of reactive cellophane covered by a layer of nonreactive cellophane over the aneurysm. The patient died fifteen and a half months after operation from rupture of the aneurysm into the duodenum with massive gastrointestinal hemorrhage.

Blakemore[141] has presented an account of progressive constrictive occlusion of the abdominal aorta with wiring and electrothermic coagulation. The heating of the wire above the heat coagulation point of blood proteins causes deposition on the wire of tenacious, clot-stimulating protein coagulum. Only the wire in the recesses of the aneurysm becomes hot enough to cause clotting, the wire crossing the fast moving blood current of the aorta being cooled too rapidly to stimulate clotting. Thus, only concentric clotting is deposited. In 8 cases of arteriosclerotic fusiform aneurysms gradual occlusion took place, and collateral circulation developed. Blakemore[142] reports a later series of 32 cases, with 8 deaths, or 25 per cent, from rupture. Linton[155] has wired 25 abdominal aneurysms by the "pack" method. Six of these procedures were done shortly after rupture of the aneurysm occurred. Three of these 6 patients died within a week, but 2 others survived for fourteen and eighteen months, and 1 was living and gainfully employed at the time of the report two and a half years after the operation. Seven patients in the entire group died after being discharged from the hospital. They lived for varying periods from a month to two and a half years. Ten

patients, or 40 per cent, were still alive after wiring, after a month to two and a half years.

Stone and Lord[158] state that magnesium wire is approximately twice as thrombogenic as stainless-steel wire when placed in the abdominal aortas of dogs. They recommend for clinical use an alloy of magnesium wire containing 2 per cent aluminum as being less brittle and having even a greater thrombogenic tendency than the untreated magnesium wire. In discussing the surgical treatment of arteriosclerotic aneurysms of the abdominal aorta, DeTakats and Marshall[145] report their experiences with 10 cases in which the principles of intrasaccular wiring, perisaccular production of fibrosis, proximal banding or a combination of these methods was carried out. Four patients in the group were alive and had improved for a period of one to four years. All of another group of 7 patients, not operated on, were dead.

A series of 12 cases of aneurysm of the abdominal aorta treated by resection and restoration of continuity with homografts was reported by DeBakey and Cooley,[144] with 1 death thirteen days postoperatively from uremia and secondary hemorrhage. It is interesting that 5 of the aneurysms had been wrapped with polythene film seven to forty-one months previously with progression in symptoms and enlargement of the aneurysm. Linton[156] wired aneurysms of the thoracic aorta in 18 patients, with 4 early and 9 late deaths. Five living patients survived for six months to four years, with relief of pain and other symptoms.

Lam and Aram,[152] reported a case of resection of an aneurysm of the descending aorta with restoration of continuity by means of a homologous aortic graft. The death of the patient three months later was due to sepsis occurring in an old aneurysm sac, which had been left in situ. In the following year Cooley and DeBakey[143] presented a series of 6 cases of intrathoracic aneurysms of the aorta and great vessels treated surgically. Fusiform aneurysms of the subclavian and innominate arteries, as well as a saccular aneurysm of the transverse aortic arch, were excised. Another saccular aneurysm of the transverse arch was ligated at its base with a rubber catheter. This patient died of fatal hemorrhage two months later. Two other aneurysms of the thoracic aorta were treated, by cellophane wrapping in 1 patient and by wrapping, wiring and aneurysmorrhaphy in the other. The latter died of hemorrhage eighteen days after operation. Bahnson[140] reported 8 patients with saccular aneurysms in different regions of the aorta treated by excision of the sac and suture of the aorta. There were 2 deaths, both related to the operation.

The treatment of arteriosclerotic popliteal aneurysms by a preliminary lumbar sympathectomy followed by extirpation, described by Linton[154] in 1949, with good results in 13, or 93 per cent of 14 patients, has been corroborated by Janes and Ivins,[150] who report 8 patients, with 9 aneurysms, treated successfully. Arteriograms gave accurate information on the size and location of the aneurysm and the state of the vessels distal to it.

Gifford, Hines and Janes,[147] in an analysis and follow-up study of 100 popliteal aneurysms, found that of 21 patients with popliteal aneurysms not treated by extirpation or obliteration, only 5 were without complications at the end of five years. On the other hand, in 23 treated surgically, no complications were found at the end of approximately six years. Eighteen of the 20 amputations, which had to be done because of complications, were performed in the patients not treated surgically.

In a few cases the insertion of a venous or arterial graft to bridge the defect in the popliteal artery has been found necessary to preserve the limb, but in many of the cases without the use of a graft the collateral circulation becomes augmented to such a degree that palpable pulsations return in the dorsalis-pedis and posterior-tibial arteries. The decision whether to graft or not must usually be made at the operating table and will depend on the condition of the proximal and distal ends of the popliteal artery, as well as the findings by arteriography. This method will probably be used more and more to avoid the immediate postoperative disability of intermittent claudication observed in the cases in which the arterial continuity is not restored.

Sir Gordon Gordon-Taylor[148] has comprehensively reviewed the subject of innominate-artery surgery, with special reference to aneurysm. A list of the surgeons who are known to have placed ligatures around the innominate artery is presented in chronologic order, from 1818 to 1949. The author describes 7 cases of his own and adds 22 unpublished cases to the literature. Another case was reported by Kirby and Johnson.[151]

The existence of a tortuous right common carotid artery, which may simulate an aneurysm, has been described again by Deterling.[146] Eighty-nine cases collected from the literature were reviewed, and 21 additional ones were presented. The lesion appears to develop as a result of elevation of the aortic arch and is found chiefly in women with diastolic hypertension. Treatment should be aimed at modifying the hypertension, since troublesome local symptoms are rare.

Dissecting aneurysm of the aorta remains a grave problem. Levinson et al.,[155] in an account of 58 autopsied cases, report that 21 patients with acute cases died in one to forty-eight hours, 22 with the subacute type lived three to sixty days, and 15 with the chronic, or healed, type survived for three months to eight years.

In general it can be stated that the best method of treating aneurysms of the abdominal aorta distal to the renal arteries, as well as those involving the iliac, femoral, popliteal, subclavian, brachial and carotid arteries, is extirpation of the aneurysm with restoration of the arterial continuity by the use of some type of blood-vessel graft. Aneurysms of the aortic arch,

descending, thoracic and upper abdominal aorta may, in some cases, be partially resected, aortic continuity being maintained. The method of intrasaccular wiring should be used for some of the aneurysms of the thoracic aorta because of the good results obtained, with a relatively low operative mortality.

Arteriovenous Fistula

In a careful study of 101 cases of traumatic arteriovenous fistulas and aneurysms in Korean War wounded Seeley et al.[158] recommend re-establishment of arterial continuity by suture anastomosis, homologous artery graft or autogenous vein graft.

In arteriovenous fistulas of relatively short duration, according to Gerbode and his associates,[162] procedures that restore arterial continuity should be used when ever they are technically feasible. This conclusion is based on a study of 27 arteriovenous fistulas and aneurysms resulting from instruments of war. In 13 extremities ligation alone was used, and 7 of these patients had clinical evidence of circulatory impairment.

In arteriovenous fistulas of many years' duration that involve the great vessels of the lower extremities reconstructive procedures are hazardous because of the arteriosclerosis and calcification at the site of the fistula. In addition severe dilatation and thinning of the artery supplying such fistulas may produce an aneurysm proximal to the fistula even if quadruple ligation or reconstruction of the artery has been accomplished.

Holman and Taylor[165] state that fistulas, with or without symptoms, must be eliminated to avoid the inevitable, though sometimes long-delayed, cardiac dilatation and decompensation that follow a progressive increase in volume flow through the fistulous circuit. Significant advances in the understanding of the pathological physiology of arteriovenous fistulas have been made by Holman,[164] Freeman et al.,[161] Shumacker and Stahl,[167] Bosher and his associates[160] and Hammer and his co-workers.[163]

(To be concluded)

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Peripheral Arteriosclerosis

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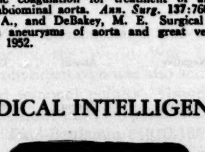
MEDICAL INTELLIGENCE



PRIMARY HYPERPARATHYROIDISM

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THAT primary hyperparathyroidism[1] is no longer rare is evident from the recent literature.[1-4] It is equally apparent that the diagnosis will not be made unless a systematic search is undertaken to discover patients with this entity. To re-emphasize this point, which has been made previously and well outlined by Keating and Cook,[5] and to follow the suggestion of Norris[6] that all cases of hyperparathyroidism in the next ten years be reported, the experience at the Hitchcock Clinic is recorded.

Before 1948 only 1 case of hyperparathyroidism had been discovered at this institution. This patient was referred to Dr. Fuller Albright, of the Massachusetts General Hospital, in 1938, who has reported the case. In the last five and a half years this diagnosis has been confirmed by operation and excision of adenomas in 7 patients. This abrupt apparent change in frequency is considered due not to an actual increase but to greater awareness that the disease exists and can be found if one searches for it. A similar experi-

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ence was noted by Keating and Cook.[5] However, Ferrebee,[7] after investigation of this problem at the Mary Imogene Barrett Hospital in Cooperstown, New York, states that he has been unable, during a comparable period, to make this diagnosis. The exstudies are made in each case, of course. Serum alkaline phosphatase is determined but is of little assistance diagnostically. A bone biopsy showing a giant-cell tumor-like formation is highly suggestive. However, a modified urinary calcium balance[8] is the most profit-

TABLE 1. *Pertinent Chemical Data.*

PATIENT	CALCIUM	PHOSPHORUS	SERUM TOTAL PROTEIN	BLOOD UREA NITROGEN	SERUM ALKALINE PHOSPHATASE	URINARY CALCIUM
	mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*Bodansky units*	*mg./hour*
S.P.	13.5	2.6	7.4	24	13.4	150,120,120
I.M.	11.2	3.2	6.7	14	—	230,200,205
R.M.	14.8	4.8	6.4	34	5.7	—
A.T.	14.0	2.4	6.3	—	2.3	540,700,630
H.L.	12.4	2.5	7.1	12	3.2	350,320,270
E.P.	12.5	2.5	6.8	9	1.1	—
A.B.	11.3	4.1	5.6	80	4.4	(50 per day)

planation for this anomalous situation is not apparent.

Patients with renal and ureteral calculi are the largest single source of potential cases of hyperparathyroidism. In the period encompassed by this study, 302 patients with ureteral or renal calculi were examined, but out of this group only 4 were ultimately proved to have hyperparathyroidism—a frequency of 1.3 per cent. Two patients showed bone lesions that led to the diagnosis, and 1 other was discovered when an otherwise unexplained renal insufficiency was demonstrated.

The technic of study must of necessity be individualized. Serum calcium, phosphorus and protein able single procedure to clinch the diagnosis. In spite of definite variations of the calcium content of the diet in various locales and seasons[9] an adenoma has been demonstrated when a patient has been on the diet outlined and has shown hypercalciuria. The calcium balance study is easily and satisfactorily accomplished in outpatients.

TABLE 2. *Pertinent Clinical Features.*

PATIENT	YEAR OF STUDY	AGE	PRESENTING COMPLAINT	SUGGESTIVE MANIFESTATIONS	X-RAY STUDY OF BONE	PALPABLE ADENOMA	PRESENT STATUS
		yr.					
S.P.	1948	47	Intermittent claudication	Cystic bone lesion; giant-cell tumor.	Positive	Present	Patient dead of cerebral hemorrhage
I.M.	1949	46	Stones; recurrent urinary infection.	Abnormal blood chemical constituents	Negative	Absent	Good; increased strength, with slight hypertension.
R.M.	1949	53	"Anorexia nervosa"	Renal insufficiency; hypertension; abnormal blood chemical constituents.	Negative	Present	Patient improved symptomatically; renal function improved; hypertension.
A.T.	1951	18	Renal stone	Abnormal blood chemical constituents	Negative	Absent	Urinary infection; 2 small stones.
H.L.	1951	52	Renal stone	Abnormal blood chemical constituents	Negative	Absent	Poor; angina present; intermittent claudication.
E.P.	1952	44	Recurrent renal stones	Abnormal blood chemical constituents	Negative	Absent	Good
A.B.	1953	62	Fracture of clavicle	Cystic bone lesion; giant-cell tumor.	Positive	Present	Fair; hypertension; angina; renal insufficiency.

Table 1 presents the pertinent chemical data that were of value in the preoperative diagnosis. For the most part these represent average figures of several determinations.

The urinary calcium excretion in patient S.P., which was within the normal range, may have rep-

resented mild renal insufficiency or possibly a technical error. The extremely low calcium excretion in the last patient, A.B., was due partly to a severe renal insufficiency and partly to human albumin, which was given intravenously during the balance study as part of another investigation.

Table 2 demonstrates certain clinical features of interest. The finding of a palpable mass in the neck of 3 patients was surprising. The demonstration of an altered vascular system in 5 out of the 7 was disturbing. It is hoped that earlier diagnosis will prevent this complication.

Summary

The results of a search for patients with hyperparathyroidism is briefly presented. The disease is not rare, and simple technics to assist in diagnosis are suggested.

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DOCTORS AFIELD

Georges Clemenceau

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PIERRE-Paul Clemenceau (1749-1825), great-grandfather of the World War I premier of France, was a physician who was also active in village, communal and national politics. Grandfather Paul-Jules Benjamin, born in 1777, practiced medicine all his life; father Paul-Benjamin (1810-1897), who was also a physician, after the age of forty devoted himself to music, painting and sculpture. An excursion into conspiratory politics resulted in his deportation to Algeria in 1858. Son Georges (aged seventeen) dashed through the cordon of guards who were taking his father from prison to exile, exclaiming, *"Je te vengerai, père"* — a scene worthy of antiquity, in the words of an enthusiastic biographer.[1]

Georges Clemenceau (1841-1929) entered the school of medicine at Nantes in 1858, served an internship at the Hôpitaux de Nantes and opened an office in Paris in 1861. In the following year he was sentenced to seventy-seven days in jail for inciting the workers of Sainte-Antoine to celebrate the anniversary of the Republic. In 1865 he submitted a 224-page thesis, *De la génération des éléments anatomiques,* — "a dull polemic in defense of materialistic monism" (Bruun[2]) — and received his diploma from the Faculty of Medicine of the University of Paris.

His characteristically frank, if not precisely scientific, preamble was: "The opinions I express are my own. I do not have them as a result of this work; I have done this work because I have these opinions."

The following year found him in the French colony of New York's Greenwich Village, where he had gone, according to Alexander Woollcott, "to make his fortune and see the world, I suppose, but more particularly to escape from a France ruled by a rouged Napoleon, sitting on the nervous edge of a recent throne."[3]

It is said that his nimble wit, his horsemanship and his skill with sword and pistol, supplemented by an elaborate wardrobe from his Parisian tailor, fitted him to play the part of the romantic foreigner, but that, socially, his American adventure remained a comedy of manners that lacked sincerity and substance.[4]

In 1867, when he was teaching French and equitation "to a school of young misses in Stamford, Connecticut, and desired, or at any rate agreed, to marry one of his pupils" (Mary Plummer), it was to Woollcott's grandfather that he went "to borrow the cost of his wedding trip and the price of a fine new suit of clothes."[3]

Back in France, he settled in Montmartre in 1869. He took no military part in the Franco-Prussian war, but after the revolution of 1870 he became mayor of the unruly eighteenth *arrondissement* of Paris, and was off to a lifetime of feverish political and journalistic activity.

His marriage to Mary Plummer lasted only seven years. A separation, based on irreconcilable differences of temperament, was arranged, and the pair were never reunited.

In 1880 he founded the newspaper *La Justice,* the principal organ of Parisian radicalism. It was in considerable part owing to his reporting of the facts in the Dreyfus affair during the '90's that public interest was aroused. Clemenceau supported Zola (1898) and opposed the anti-Semitic and Nationalist campaign. His efforts to rectify matters were not complete until Dreyfus was finally exonerated in 1906.

In 1907-1908 Clemenceau became premier of France. It was at this time that he played an important part in cementing the new entente with England.

As a senator in 1914 at the outbreak of the war with Germany, for three years it became his daily habit to rise at one or two in the morning, light his lamp and write intensely for three or four hours on his daily newspaper article of two columns. At 6 or 7 o'clock he ate breakfast, performed calisthenics under the supervision of his physical instructor and received his daily flow of visitors. Then he attended to his correspondence of 100 or 200 letters a day and, after a hasty lunch, went to the Senate. His legisla-

tive functions accomplished, he went to his newspaper office, conferred with his subeditors, read the papers and, at eight o'clock in the evening, returned home, ate dinner and went to bed.

In November, 1914, he again became premier. How he carried his country through the war is a comparatively recent memory. From November, 1918 to June, 1919, he devoted himself to the international settlement that laid the groundwork for World War II. He forced his views alternately on President Wilson and Mr. Lloyd George, with whom he was less than sympathetic. *"Ah, si je pouvais pisser comme il parle!"* he is said to have remarked, somewhat irritably, of the Prime Minister on returning to the council chamber during the peace negotiations, perhaps partly because of his increasing prostatic obstruction.

In 1921 he retired to his books and his rose garden, but in 1922 he visited the United States on a four-week lecture tour, speaking in defense of the French proposal to invade the Ruhr valley in an effort to compel German reparations payments. In 1925 he was busy writing a philosophical treatise and a life of Demosthenes. He died in 1929 at the age of eighty-eight.

Clemenceau was the father of a son and two daughters. A grandson, M. Jacquemaire-Clemenceau, was wounded while serving as an infantryman at Verdun in 1914 and at Les Éparges in 1915. He subsequently became an aviator, and received three citations and the military medal. After the war he studied medicine; his thesis was published in 1926. He died at the age of thirty-seven from an infection acquired in the operating room, two years after the death of the old Tiger.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 40351

PRESENTATION OF CASE

First admission. A sixty-six-year-old housewife was admitted to the hospital because of abdominal pain.

Thirty-six hours previously severe right-upper-quadrant pain had suddenly begun, radiating around the right costal margin to the back. She denied chills and fever but had vomited once.

The past history revealed that six months before admission she had palpitations and "skipping heart," with moderate dyspnea on climbing three flights. She was given 1 tablet of digitalis every day until three days before admission. There was no ankle edema, nocturnal dyspnea, known hypertension or diabetes. She had lost 20 pounds gradually over the past three years but denied tremor, heat intolerance or increased appetite. On careful questioning there was no history of rheumatic fever.

Physical examination showed an obese woman who complained of pain in the upper abdomen. The neck veins were flat. The thyroid gland was not palpable, and the lung fields were clear. The heart had its point of maximal impulse 9.0 cm. to the left of the midsternal line at the midclavicular line. There was a Grade 2, apical, systolic murmur and a totally irregular rhythm. The aortic second sound equaled the pulmonic. The abdomen was tender in the right upper quadrant, with spasm but no masses. There was no ankle edema.

The temperature was 101.2°F., the pulse 128, and the respirations 12. The blood pressure was 150 systolic, 100 diastolic.

Urinalysis gave trace tests for albumin and bile. The sediment contained 8 to 12 white cells per high-power field. Examination of the blood revealed a hemoglobin of 14 gm. per 100 cc. and a white-cell count of 8000, with 77 per cent neutrophils. Serum bilirubin, fasting blood sugar and serum amylase were normal. An x-ray film of the chest demonstrated clear lung fields except for slightly prominent hilar regions. The heart shadow was larger than usual, with probable enlargement in the regions of the left ventricle and left atrium. An electrocardiogram showed atrial fibrillation at a rate of 140, right-axis deviation, very small R and deep S waves in Leads 1 and aVL, normal R and S progression in the precordial leads, a slightly elevated ST segment and a small, upright T wave in Leads 1, aVL and V_1 and a slightly depressed ST segment and inverted T wave in Leads 3, aVF and V_6.

After further digitalization with Cedilanid, cholecystectomy for acute cholecystitis and cholelithiasis was performed. The patient recovered uneventfully and was discharged on the ninth hospital day.

Second admission (ten days later). She was admitted to the overnight ward because of sudden coldness and pallor of the right leg.

Just after she awoke and while she was walking the right leg had suddenly become cold and white below the ankle and was numb, "like walking on bone." It was not painful, but she could not move the foot or toes. During the day function returned, but hospitalization was advised.

Physical examination revealed clear lung fields; the heart had an irregular rhythm. The aortic second sound equaled the pulmonic, and two competent observers heard no murmurs. The cholecystectomy scar was well healed. There were no pulsations below the right femoral artery, and the skin was slightly cooler below the knee than elsewhere. The vital signs and laboratory data were unchanged.

She was given Tromexan and Dicumarol, with subsequent lowering of prothrombin-activity to levels of 15 to 45 per cent of normal. Function returned to the right foot, and a faintly palpable right dorsalis-pedis pulse was present. Two days after admission a cardiologist described a definite Grade 3, mid-diastolic rumble at the cardiac apex, with presystolic accentuation; this murmur was inconstant. She was discharged on the third hospital day to continue on Dicumarol as an outpatient.

Third admission (two weeks later). She was admitted in an attempt to restore the cardiac rhythm to normal with quinidine. She had no symptoms.

The heart was described as having its maximal impulse 10.5 cm. to the left of the midsternal line. The first mitral sound was accentuated, and there was a Grade 2, apical, diastolic rumble. The pulmonic second sound was slightly accentuated and greater than the aortic. The liver edge was percussed 2 fingerbreadths below the right costal margin, and there was equivocal ankle edema. Vital signs and laboratory data were as before, with an irregular pulse at a rate of 72.

She was continued on digitoxin, 0.15 mg., and was given quinidine sulfate, 0.4 gm. every two hours for ten hours. The next morning the rhythm was unchanged, and three additional doses were given. The evening of the second day there was sinus rhythm at a rate of 88. She had four or five watery stools that night, and the next morning some coupling of ventricular premature beats was observed. She was discharged to continue the program of low-sodium diet and digitoxin, 0.1 mg., Dicumarol, 50 mg., and quinidine, 0.2 gm., four times a day.

Fourth admission (twenty-two months later). In the clinic, thirteen days after discharge, the rhythm was again one of atrial fibrillation, and she had had diarrhea. Both quinidine and Dicumarol were stopped. Since then she had been followed in the clinic and was getting along well. About three weeks before this entry she had an episode of faintness while standing that went away when she sat down. She did not lose consciousness, nor did the symptoms return after she felt well again. On the morning of admission, while shopping, she noted the sudden appearance of severe pain in both legs. After about an hour the right leg felt normal, but the left had loss of some sensation and was very painful.

On physical examination the lung fields were clear; there was atrial fibrillation and a short, apical, systolic murmur. A Grade 2, apical, diastolic rumble was heard, and the pulmonic second sound was greater than the aortic. No peripheral pulse below the left femoral artery was felt, but the right popliteal pulse was normal. A pedunculated rectal polyp was discovered. Vital signs and laboratory data were unchanged.

A left-femoral-artery embolectomy was performed. The left popliteal pulses were good thereafter. She did well, and later two benign adenomatous polyps were removed from the rectum. She was discharged on the twelfth hospital day.

Final admission (twelve days later). She was readmitted to the hospital because of the sudden onset of severe pain in the lower abdomen and inability to move either extremity.

These symptoms began during the morning of admission while she was in bed. The initial symptoms persisted, and numbness with aching developed. She also had difficulty in breathing and was orthopneic.

On physical examination, she was pale, sweaty, cold and in acute distress. The neck veins were distended, and expiration was prolonged. There were rales in the posterior lung field. The heart findings were unchanged. The abdomen was soft, with peristalsis audible and the aortic pulse palpable at the umbilicus. The skin was cooler below the umbilicus. The lower extremities were cold, pale and lifeless, without sensory or motor function.

The temperature was 99°F., the pulse 100 and irregular, and the respirations 30. The blood pressure was 180 systolic, 100 diastolic.

Urinalysis gave a ++ test for albumin, with a few clumps of white cells in the sediment. The blood hemoglobin was 13.5 gm. per 100 cc., and the white-cell count 17,000, with 74 per cent neutrophils.

A saddle embolus was removed from the aortic bifurcation, and femoral pulsations returned at once. Immediately after operation both legs were cyanotic to the midcalf, but the blood pressure was stable; the pulse was 100, and the temperature 102°F. She became slightly cyanotic, with clammy skin and tachypnea, and coarse rales were present bilaterally. She was kept in the orthopneic position. There was almost no urinary output in the postoperative period. The blood pressure began to fall gradually to ranges of 90 systolic, 70 diastolic, to 70 systolic, 50 diastolic, and the pulse was rapid and weak. She became unresponsive to all stimuli except palpation of the abdomen, which caused her to wince. She died twenty-four hours after operation.

Differential Diagnosis

Dr. Allan L. Friedlich*: For the purposes of the discussion we can forget about the cholecystitis and rectal polyps and consider the problem of a sixty-six-year-old woman with atrial fibrillation. There was no clear evidence of any coronary-artery disease to account for the development of the fibrillation. The patient's physicians were obviously considering thyrotoxicosis as a cause because she was questioned carefully in this regard. There was a 20-pound weight loss that was unexplained. We know that thyrotoxicosis sometimes exists, particularly in elderly patients, with few or no symptoms or signs. The diagnosis is occasionally made only by studies with radioactive iodine or a determination of serum protein-bound iodine. This is a situation that we must constantly be on the lookout for, but I think that in this case we can dismiss thyrotoxicosis as the cause of the fibrillation, which I believe to have been due to rheumatic heart disease, with mitral involvement. The auscultatory findings in this patient were quite variable: at times there were no murmurs; at other times there was a Grade 2, apical, systolic murmur, and at still others there was a Grade 3, apical, diastolic rumble. I wonder whether there was actually any presystolic accentuation to this murmur because this would be unusual in the presence of atrial fibrillation. There is, then, presumptive evidence of rheumatic involvement of the mitral valve.

The next problem is to assess the degree and variety of mitral involvement. Does mitral stenosis of severe degree ever occur when there is no murmur of mitral stenosis or only a transient murmur of mitral stenosis? In the last few years, since becoming particularly interested in this problem, we have seen a number of such patients who have a high degree of mitral stenosis and in whom the diagnosis had to be suspected on other evidence because no murmur was present. In these patients the diagnosis of mitral stenosis was confirmed by cardiac catheterization, mitral-valve surgery or autopsy. Since we are told nothing about any episodes of acute pulmonary edema or hemoptysis in this patient's past the chances of her having an extreme degree of mitral stenosis are not great. At this point it might be well to look at the x-ray films.

Dr. John F. Gibbons: Films apparently were taken at the time of the first admission and were never repeated on subsequent admissions. At this time the size of the heart shadow is not very striking, although there may be some enlargement of the left ventricle and there is a prominence in the pulmonary-artery segment of its left border. I do not have any information about the fluoroscopic examination, but on these films I do not believe I can say that the left atrium is enlarged; it could be slightly enlarged. The lungs and the pulmonary vascular shadows are normal.

Dr. Friedlich: Do you not think this is an enlarged left atrial appendage?

*Assistant physician, Massachusetts General Hospital.

Dr. Gibbons: Yes; I think one would assume that it is; one would have to see the fluoroscopic examination and take other views of the chest to be sure.

Dr. Friedlich: Is that a double contour due to a large left atrium?

Dr. Gibbons: I cannot see any. I think one could "imagine" one.

Dr. Friedlich: The next point in helping to assess the presence or absence of mitral stenosis is the electrocardiogram. I took the liberty of looking at the tracing itself. This was described as showing marked right-axis deviation, which is in favor of mitral stenosis with resultant added load on the right ventricle and no added load on the left ventricle. Inspection of the electrocardiogram, however, demonstrates that the right-axis deviation was an artifact produced by the switching of the arm leads. It is still possible to interpret the electrocardiogram with that in mind. There is no clear-cut hypertrophy of the right or left ventricle.

Can a considerable degree of mitral stenosis be present without evidence of right-ventricle hypertrophy? The answer to that question is certainly yes. We have seen a number of patients who were successfully operated on for severe mitral stenosis in whom hypertrophy of neither the left nor the right ventricle was seen in the electrocardiogram. We must also bear in mind the fact that this patient was mildly hypertensive. Therefore, the slight hypertrophy of the left ventricle produced by hypertension could well have balanced right-ventricle hypertrophy caused by mitral stenosis, thus leading to a normal-looking electrocardiogram.

The crux of this problem is the impressive number of emboli that this patient had, doubtless arising from mural thrombi in a fibrillating left atrium. There was no evidence of myocardial infarction, with mural thrombus, or of subacute bacterial endocarditis as other sources of thrombus formation. The first embolus to the femoral artery was followed by a spontaneous recovery and was treated conservatively. Thereafter, anticoagulants were used, and an attempt was made to convert the rhythm to normal, in the hope of decreasing the likelihood of further thrombus formation. This, however, was unsuccessful. In spite of prophylactic doses of quinidine, which were sufficient to cause diarrhea, a normal rhythm could not be maintained. Two years later there was another embolus, which was removed from the left femoral artery. I am sure at that time that two therapeutic problems presented themselves: one undoubtedly was whether this patient should be treated with long-term anticoagulant therapy (this may have been impractical for one reason or another) and the other was to decide whether the patient should be operated on for mitral stenosis in the hope of preventing further emboli. Her age, sixty-six, was probably the reason that this was not more seriously considered. At the time of the final admission an embolus was removed from the aortic bifurcation. This, too, should

have been successful except for the presence of one or, quite probably, more than one complicating factor.

The last electrocardiogram taken before death was suggestive of an anterior myocardial infarction. I hesitate to bring that into the discussion because there were so many other things that may have gone wrong.

In the protocol there is a hint that the urinary output fell before the fall in the blood pressure. That, of course, raises the question of emboli wafted into the renal arteries as well as to the aortic bifurcation. However, other factors were present that could explain the oliguria.

A condition to be considered very seriously is that of an embolus to the superior mesenteric artery with infarction of bowel. This is suggested by three features: the abdominal pain, the abdominal tenderness, and the white-cell count of 17,000, which is higher than one might expect in an early uncomplicated embolus to the aortic bifurcation.

Terminally, congestion of the lungs developed, and that raises another question. Could this patient have had a ball-valve thrombus in the left atrium? This is a rare condition, but when it occurs it is usually seen in women who have mitral stenosis, atrial fibrillation and peripheral emboli. There is nothing really diagnostic of a ball-valve thrombus in the left atrium in this case. There are, however, a few hints of its presence, all of which could be explained on other grounds. The hints are the brief episode of faintness before the fourth hospital admission, the unusual variability of the murmurs and the rapid development of pulmonary congestion and profound hypotension leading to death.

In summary I shall say that the patient had slight hypertensive heart disease, rheumatic heart disease, with mitral stenosis of moderate degree, atrial fibrillation, pulmonary congestion and multiple emboli from the left atrium, probably with infarction of the bowel. I shall guess that there was a ball-valve thrombus of the left atrium, and I shall be curious to know whether there was an embolus to a coronary artery.

Clinical Diagnoses

Rheumatic heart disease.
Atrial fibrillation.
Multiple arterial emboli.

Dr. Allan L. Friedlich's Diagnoses

Rheumatic heart disease, with mitral stenosis.
Atrial fibrillation.
Pulmonary congestion.
Multiple emboli from left atrium, with infarction of bowel.
Ball-valve thrombus, left atrium.
Hypertensive heart disease, slight.

Anatomical Diagnoses

Rheumatic heart disease with mitral stenosis.
Ball-valve thrombus, left atrium.
Emboli to superior mesenteric artery, with gangrene of small bowel.
Hypertensive heart disease.

Pathological Discussion

Dr. Benjamin Castleman: The heart was slightly enlarged, but it probably was not much larger than it had been two years before. The atria were enlarged—the right was about twice, and the left perhaps three times the normal size. The right ventricle was not hypertrophied; it measured only 3 mm.; the left measured about 17 mm. I was afraid that the interpretation of right-axis deviation might have indicated to Dr. Friedlich that there was hypertrophy of the right ventricle. I am glad he found the error in the record. As Dr. Friedlich predicted the patient died of embolism to the superior mesenteric artery, with gangrene of the small bowel; at autopsy a liter of fluid was present in the abdomen. There were also recent emboli to the left kidney, and, to make Dr. Friedlich's prediction complete, there was a tiny embolus, which we saw microscopically, in one of the sections of the myocardium—not enough, however, to produce myocardial infarction. The lungs showed considerable edema, which was terminal.

Figure 1.

The orifice of the mitral valve was small, and the cusps were moderately calcified but remarkably pliable (Fig. 1). Dr. Friedlich really predicted everything because there was a ball-valve thrombus that was freely movable in the left atrium. This picture (Fig. 2) of the thrombus over the mitral valve shows how it acted as a ball valve and could obliterate the entire orifice of the mitral valve. Dr. Fairfield Goodale, in our laboratory, with Dr. Robert Shaw, of the Surgical Service, has been doing pressure-volume studies on the heart after death in all types of heart disease. They studied this heart, and I have asked Dr. Goodale to tell us his findings.

Dr. Fairfield Goodale, Jr.: Post-mortem perfusion experiments on the heart were carried out in an at-

tempt to correlate the clinical and pathological findings. The left atrium was cannulated and into it was run water at pressures varying up to the equivalent of a systolic blood pressure of 100. By then taking manometric readings from both the left atrium and the left ventricle we could calculate and graph the pressures across the mitral valve and so determine the degree of mitral stenosis. This was done both with and without the ball-valve thrombus in the left atrium. When the thrombus was not present in the atrium the degree

FIGURE 2.

of mitral stenosis was only moderate, ranging about midway between a normal and a very severely stenotic mitral valve. With the thrombus in the atrium the degree of stenosis produced by obstruction of the already damaged valve orifice by the thrombus was found to be extreme—much more striking than in even the most severe stenosis tested in the past.

By reversing the direction of water flow we could test the mitral valve for regurgitation. Thus, the aorta was cannulated, and into it was run water at pressures varying up to the equivalent of a normal systolic blood pressure. By placing the finger tip lightly in the mitral-valve orifice one could feel the leaflets close tightly as the pressure rose, so that it was possible to say definitely that in this case there was no regurgitation.

Previous work has shown that there is an excellent correlation between ante-mortem cardiac catheterization findings in cases of mitral stenosis and values obtained post mortem on the same hearts by this perfusion technic. Both this work and the clinical history suggest that, owing to swirling blood currents in the fibrillating left atrium, the ball-valve thrombus in the present case only rarely added to the moderate degree of mitral stenosis already present. The degree of stenosis that it produced when it did drop into the valve orifice was so severe as to have been incompatible, except momentarily, with life.

DR. CASTLEMAN: We selected this case, hoping that, given all the murmurs in detail, the changes in them and the other manifestations, Dr. Friedlich would be able to make the diagnosis. This diagnosis is very rarely made before death, especially in a patient who does not have all the characteristic findings. Dr. Arias,* who worked in the cardiac laboratory last year, studied the 13 cases of ball-valve thrombus in this hospital and the 42 described in the entire literature. His statistics are interesting in that the sex is preponderantly female—43 females to 7 males, or a ratio of 6:1. At the same time out of 448 post-mortem cases of mitral stenosis in this hospital the ratio of females to males was 1.9:2.6, so that the factor is not just mitral stenosis.

*Arias, L. Unpublished data.

CASE 40352

PRESENTATION OF CASE

A thirty-year-old single woman entered the hospital because of fever.

Three weeks previously she had had an episode of fever, which subsided with penicillin injections. A week later the fever recurred, this time associated with chills, and again subsided in three or four days with penicillin, sulfonamide and chlortetracycline therapy. Three days before admission she again had chills, and the temperature rose to 104°F. The fever and chills continued up to the time of admission. Blood and urine cultures a week before admission were said to show no growth. She had had no antibiotic therapy for two days before admission. During the previous four weeks she had a weight loss of 15 pounds attributed to anorexia. There was no known exposure to any infectious disease. She had not ingested any unpasteurized milk, suspicious water or food or poorly cooked pork. There was no history of headaches, abdominal pain, sore throat, respiratory or middle-ear infection or urinary-tract symptoms such as dysuria, hematuria and pyuria. There were no joint, muscle or bone pains. She had had no rashes or edema. There was no past history of rheumatic fever. She had never been outside the United States. There was no history of drug ingestion or exposure to solvents with vapors of any kind.

Physical examination revealed a well nourished, pale woman. Prominent, nontender cervical lymph nodes were palpable on the right, the largest of these measuring 2 cm. in diameter. No other adenopathy was noted. The spleen was palpable 2 cm. below the left costal margin and was soft. The liver edge was just palpable and was slightly tender. A Grade 1 systolic, apical, cardiac murmur was heard. There were no petechiae. Examination of the optic fundi was negative.

The temperature was 104°F., the pulse 130, and the respirations 30. The blood pressure was 105 systolic, 65 diastolic.

Examination of the blood disclosed a hemoglobin of 6.8 gm. per 100 cc. and a white-cell count of 3200,

with 57 per cent neutrophils, 19 per cent lymphocytes, 5 per cent monocytes, 17 per cent young neutrophils, 1 per cent late myelocytes and 1 per cent unclassified cells. There was slight variation in the size of the erythrocytes as well as slight achromia. The platelets appeared normal in the peripheral blood smear. The reticulocyte count was 0.6 per cent. The nonprotein nitrogen was 20 mg., and the serum uric acid 1.6 mg. per 100 cc. X-ray films of the chest were normal, and a tuberculin test (first-strength purified-protein derivative), an "L.E." preparation and a Coombs test were negative. A catheterized urine specimen gave a ++ test for albumin; the sediment contained 2 red cells, 15 white cells, frequent granular casts and a moderate number of bacteria per high-power field. Culture of the urine grew out rare colonies of *Staphylococcus aureus;* a direct smear showed rare gram-positive rods. Blood cultures obtained on the first, third, twelfth and thirteenth hospital days showed no growth. Agglutination tests for brucella, paratyphoid A and B and typhoid H antibodies, as well as heterophil agglutination tests, were negative; the test for typhoid O was positive in a dilution of 1:20, equivocal in a dilution of 1:40 and negative in a dilution of 1:80. Two stool specimens were negative for occult blood, and a stool culture was negative for enteric pathogens.

On the fourth hospital day a sternal-marrow biopsy demonstrated hyperplasia of both the myeloid and the erythroid series, with no myelosclerosis, several areas of fibrosis, an increase in the number of megakaryocytes and normal maturation of the myeloid series; no tubercles were found. Blood transfusions raised the hemoglobin level to 12.4 gm. per 100 cc. The course was febrile, the temperature rising steadily to 105.4°F. on the second hospital day and again gradually rising to 105°F. on the twelfth hospital day, when the spleen seemed larger and firmer and the cervical lymph nodes more prominent. The peripheral blood picture remained the same, with the highest white-cell count recorded at 5000, with 82 per cent neutrophils, 6 per cent young neutrophils, 2 per cent late myelocytes and 10 per cent lymphocytes. Cortisone therapy, 25 mg. orally every six hours, was begun on the eleventh hospital day. Early on the morning of the fifteenth hospital day the patient complained of the sudden onset of severe abdominal pain associated with the sensation that "something just turned over." The pain persisted and was associated with nausea and a desire to defecate. She was unable to localize or characterize the pain well but pointed to the left upper and right lower quadrants, as well as to the region of the umbilicus. She also complained of feeling "numb" in the abdomen. Physical examination at this time showed her to be pale, sweaty and apprehensive. There was no jaundice. The blood pressure was 80 systolic, 60 diastolic, and the pulse 120. The abdomen appeared slightly protuberant, and there was some periumbilical tenderness. The liver and spleen, which were nontender, were just palpable. Peristaltic sounds were heard. Rectal examination revealed a relaxed sphincter and some soft fecal material that was negative for occult blood. She gradually became unresponsive and died two hours after the onset of the abdominal pain.

Differential Diagnosis

Dr. Farahe Maloof*: In summary this thirty-year-old woman had a remittent fever, hepatosplenomegaly, cervical lymphadenopathy, a blood picture characteristic of hypersplenism and urinary abnormalities. She had an acute abdominal catastrophe, which resulted in death in two hours, five weeks after the onset of her illness. I must say at the outset that I am still not sure what the diagnosis is in spite of the excellent work-up and the wealth of evidence presented. I should like to see the x-ray films first.

Dr. C. C. Wang: The first examination of the chest shows normal lung fields and a heart that is not enlarged. The hilar and mediastinal shadows appear normal. The left leaf of the diaphragm is slightly higher than usual, suggesting some splenic enlargement. Examination of the chest approximately ten days later discloses no change.

Dr. Maloof: Is there any evidence of tuberculosis in the lungs or calcification in the neck?

Dr. Wang: There is no definite evidence of localized active disease in the lung fields or calcification in the neck.

Dr. Maloof: The bones?

Dr. Wang: The bones are normal.

Dr. Maloof: I shall divide the discussion into three parts, covering what appear to be the most important features: the fever, the hypersplenism and the terminal event. In the differential diagnosis of fever of unknown origin, we should consider infections, drugs that are used to treat infections, neoplasms and various exotic diseases. I shall not attempt to discuss in detail all the infections that might have caused this picture, for many of these have been fairly well ruled out. All the agglutinations and the stool cultures were negative; since there was no other evidence for any of these diseases I shall dismiss them without going through a differential consideration. However, in spite of the negative tuberculin test and the apparently normal roentgenogram of the chest, miliary tuberculosis remains a possibility. With the enlarged lymph nodes, the splenomegaly and the terminal catastrophe that may have been a ruptured spleen, one wonders about infectious mononucleosis in spite of the negative heterophil-antibody agglutination. However, I find it difficult to make this diagnosis on the basis of the evidence at hand. This patient had apparently not been outside the United States so she probably did not have one of the parasitic infections that cause splenomegaly, with a picture of hypersplenism. With the urinary findings, one

*Assistant in medicine, Massachusetts General Hospital.

might consider pyelonephritis, bacteremia and acute bacterial endocarditis, but these conditions would not explain the adenopathy or the blood changes, and the cardiac murmur is certainly insignificant. Furthermore, she apparently had no urinary symptoms. The previous antibiotic therapy may have been responsible for the negative blood cultures. No mention was made of the blood Hinton reaction, and hence I shall assume it to have been negative.

Neoplasms of the liver and kidney may produce unexplained fever, but I have no basis for making either diagnosis. With the urinary findings, one should consider nephritis especially since it is listed as a cause of hypersplenism; I am unable to explain the entire picture by nephritis. Of all the so-called collagen diseases disseminated lupus erythematosus seems to be the most likely. The patient was a woman and was in the proper age group, and all the findings noted in the protocol are seen in lupus erythematosus. I must confess that, until last night, I considered this as the most likely diagnosis. The absence of skin changes is not against it; however, with no arthritis and no serositis this diagnosis was finally cast aside.

One of the striking features in the protocol is the evidence for hypersplenism — the anemia, the persistent leukopenia and the hypercellular bone marrow. The severe anemia deserves a word of comment; there is no evidence of blood loss or hemolysis as judged by the blood smear and the negative Coombs test. The normocytic, slightly hypochromic blood picture with this degree of anemia is consistent with hypersplenism. In Dameshek's[1] excellent monograph on hypersplenism one finds that whenever there is hypersplenism and lymphadenopathy one should consider tuberculosis, sarcoidosis, leukemia and lymphoma. Tuberculosis was considered here since tubercles were looked for in the bone marrow. An analysis of a large series of cases of miliary tuberculosis by the group at the Boston City Hospital[2] revealed that tubercles were found at autopsy in the bone marrow of 84 per cent of such patients. I am still unable to rule this diagnosis out completely. It is difficult to make a diagnosis of sarcoidosis in the absence of skin lesions or pulmonary changes. Leukemia of any sort is ruled out by the absence of primitive cells in the bone marrow. The serum uric acid was probably ordered with this diagnosis in mind. I shall discuss lymphoma when the acute abdominal catastrophe is analyzed.

Another striking feature in the protocol is the terminal abdominal catastrophe. Apparently, up until this time, the diagnosis was not established, and cortisone treatment was instituted. The cortisone was probably given as a measure of desperation and in an attempt to overcome the inhibitory effect of the spleen on the bone marrow, possibly as a prelude to splenectomy. We are not told of any subsequent blood counts. In either event the dosage of cortisone was on the conservative side. Four days after the administration of cortisone the patient experienced severe abdominal pain, went into shock and died within two hours. Several diagnoses come to mind: ruptured peptic ulcer, ruptured spleen, massive mesenteric thrombosis, massive intra-abdominal hemorrhage and acute hemorrhagic pancreatitis. After discussing this problem with several surgeons, I am told that it would be extremely unlikely for any of these conditions except a massive hemorrhage to kill such a young patient within two hours. The stool guaiac reaction was negative; this is somewhat against mesenteric thrombosis. The supposed decrease in the size of the liver and spleen is an interesting observation and might have been related to a massive intra-abdominal hemorrhage; however, the abdominal distention and the severe pain may have precluded accurate determination of the size of these organs.

What is the relation, if any, between the cortisone treatment and this terminal event? During the administration of this drug for various diseases the following pertinent conditions have been noted: rupture of a pre-existing or an unsuspected peptic ulcer, vascular thromboses and flare-up of a latent tuberculous infection. Recently, a similar diagnostic problem was reported by MacMahon, Aisner and Patterson.[3] The patient was a thirty-two-year-old woman with an undiagnosed fever and the blood picture of hypersplenism in whom severe abdominal pain developed seven days after the administration of cortisone. At autopsy the cause of the abdominal catastrophe was found to be a ruptured lymphomatous ulcer in the jejunum. The course and findings of that patient closely resemble those of the patient under discussion. I shall end up with a diagnosis of lymphoma — reticulum-cell sarcoma — with an intra-abdominal hemorrhage from either a ruptured spleen or a ruptured upper gastrointestinal ulcer. The second possibility is miliary tuberculosis.

A PHYSICIAN: Was a smear for malaria parasites done?

DR. WILLIAM H. BAKER: It was done once. No malarial parasites were found on a thick or a thin smear.

DR. J. EHRENKRANTZ: Would you consider the possibility of an abdominal aneurysm with a rupture as the final event?

DR. MALOOF: The radiation of the pain suggested an aneurysm, but I cannot imagine that this woman had an aneurysm unless she had a mycotic aneurysm that ruptured. I do not have the evidence to make that diagnosis.

DR. BENJAMIN CASTLEMAN: The type of aneurysm that may occur in a thirty-year-old woman is usually a mycotic aneurysm.

DR. EHRENKRANTZ: I was thinking of the aneurysm with Erdheim's necrosis in the descending aorta.

DR. CASTLEMAN: That would be a dissecting aneurysm of the aorta. Certainly, the symptoms were not those of a dissecting aneurysm.

DR. JOHN B. STANBURY: Is not five weeks a short

course for a reticulum-cell sarcoma? The patient's symptoms began only five weeks before death.

DR. MALOOF: It is a short interval for many things that I considered. However, the time factor may be misleading in view of the terminal catastrophe.

DR. CASTLEMAN: What diagnosis would you make, Dr. Stanbury?

DR. STANBURY: None that Dr. Maloof has not mentioned. Of course, brucellosis comes to mind because, except for the bacteriologic studies, everything fits perfectly well. One has to think, as Dr. Maloof mentioned, of an acute ulcerative bacterial endocarditis, with emboli to the spleen and rupture, but the cardiac findings do not substantiate that. I think the diagnosis he made is as close as any that could be made.

DR. BAKER: This was a patient of Dr. Richard Whiting. I think the clinical impression went along the same lines as Dr. Maloof's. However, we did not place as much emphasis on the lymphadenopathy as the protocol did. The patient was given cortisone in desperation. No definite diagnosis had been made, and the temperature was steady at 105°F. She had been put on alcohol baths and given cold soaks in an effort to reduce the temperature, with no success. We also hoped that the number of white cells would rise. On cortisone, 100 mg. orally for two days, there was absolutely no effect so it was discontinued the day before death. We realized that, if this was an underlying miliary tuberculosis, we were endangering the patient's life, but we believed that we had to do something in an attempt to make her afebrile and operable. She presented a very confusing picture as outlined. We asked a surgeon to biopsy the cervical lymph node, but each day because of her febrile state he said, "Tomorrow."

DR. CASTLEMAN: Why did you not biopsy a lymph node originally instead of the bone marrow?

DR. BAKER: The leukopenia and the white cells in the peripheral blood on admission gave us the idea that we were dealing with a myeloproliferative disease, miliary tuberculosis or collagen disease rather than lymphoma. The lymph-node enlargement was not impressive. The only significantly palpable lymph node was one in the cervical region on the right. Only after the bone marrow gave us no positive information for diagnosis did we think about biopsying this lymph node.

CLINICAL DIAGNOSES

?Malignant lymphoma: Hodgkin's disease.
?Cerebrovascular accident.
?Ruptured viscus.

DR. FARAHE MALOOF'S DIAGNOSES

Malignant lymphoma, reticulum-cell-sarcoma type.
Ruptured spleen.

ANATOMICAL DIAGNOSES

Malignant lymphoma, Hodgkin's type, involving spleen and retroperitoneal, mediastinal and other lymph nodes.
Ruptured spleen, with massive hemoperitoneum.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed that the immediate cause of death was a vascular catastrophe; the spleen had ruptured. The spleen was quite large, weighing almost 700 gm. The abdominal cavity contained 3 liters of blood. When the blood was removed we found along the aorta masses of huge lymph nodes that on gross examination looked like malignant lymphoma, and microscopical examination confirmed this diagnosis — a characteristic Hodgkin disease.

The biopsy of the bone marrow performed before death was interesting. There was very little fat tissue and tremendous numbers of giant cells, which looked like the megakaryocytes that we ordinarily see in the bone marrow; some of those cells, however, did not look exactly like megakaryocytes. One has great difficulty, in the examination of the bone marrow in a case suspected of being Hodgkin's disease, identifying Reed–Sternberg cells when megakaryocytes are present in addition. In a case similar to this several months ago we could not be sure whether the giant cells in a bone-marrow biopsy were Reed–Sternberg cells or megakaryocytes. Dr. Edward R. Fisher, of the Cleveland Clinic, after reading this case report,[4] wrote to me saying that he had found that in 50 cases of Hodgkin's disease the Reed–Sternberg cells did not take periodic acid Schiff stain whereas the megakaryocytes did. In this case in our autopsy material we were able to show that that was true. On some of the bone-marrow sections from the autopsy material one could make the diagnosis of Hodgkin's disease; we could not make this diagnosis on the bone-marrow biopsy because of the absence of definite Reed–Sternberg cells. The other lymph nodes throughout the body were enlarged, including two in the mediastinum, but apparently not sufficiently to cast an x-ray shadow.

DR. BAKER: To my knowledge — and I have perused the literature a great deal since this patient came into the hospital — this is the first patient with Hodgkin's disease who has had a ruptured spleen as a cause of death. It occurs occasionally in infectious mononucleosis, subacute bacterial endocarditis and malaria. I asked both Dr. Frederic Parker, Jr., and Dr. Henry Jackson, neither of whom had ever seen or heard of a ruptured spleen in Hodgkin's disease. However, there is certainly no reason why it should not occur.

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GOOD FISHING

THE undergraduate editors of the *Yale Law Journal*, according to a release from the Yale University News Bureau, having performed an exploratory laparotomy on the American Medical Association, (it could hardly be called an autopsy on so active a body), have published in a recent issue of their publication a terse 84-page bulletin on their findings. The condition of the patient, the investigators report, is not so good, but recovery could take place if their advice, based on the results of a two-year-long exploration, is followed.

The Association, the editors find, is practically toxic with power; "It holds a position of authority over the individual doctor, wields a determining voice [sic] in medical education, controls the conditions of practice, and occupies a unique position of influence in shaping government health policies." Further, and more devastating, the Association does not truly represent the physicians of the nation and does not tolerate conflicting opinions inside its membership. It is, of course, obvious that the Association cannot represent nonmembers, and that it must have qualifications for membership.

Those who defy its authority, the young editors aver, are swiftly punished; overlooking the part that the completely independent state societies play in regulating the conduct of their members the writers attribute to the national organization the power of imposing professional ostracism on its fellows, interfering with their hospital advancement and jeopardizing their private practice.

A curious jumble of conclusions seems to have been reached by the embryo jurists. The real service to the nation that the Association has performed in the inspection and grading of medical schools is admitted but has been transmuted into a present control over the nation's supply of physicians, although in fact every school selects its own students and determines the numbers that it can train. It is further suggested that the Association make hospital privileges available to nonmembers, although it must be apparent that such appointments are entirely in the hands of the local governing bodies of the hospitals.

The Association, in short, is credited with a degree of despotism of which the majority of its members are completely unaware. Unwittingly they seem to be defying, defending, praising, condemning, patronizing and even at times ridiculing a power that could destroy them if it wished. Perhaps they are lulled (no play on words intended) into a false sense of security by the conviction that they are themselves the AMA, that the delegates they elect determine its policies and that through the persistent expression of their will they may bring about the removal of any of their representatives who may fall from their favor. Or perhaps the members of the Association delude themselves with the belief that their leaders,

like those of any truly democratic institution, "govern only with the consent of the governed."

It is a little unfortunate that the spokesmen of the Association, presented with so tantalizing a lure, struck at it with such vigor. Denying each unfavorable allegation point by point to the extent of using the words "false and malicious," the whole, no doubt earnest, analysis is finally branded as "an obvious attempt to neutralize the conservative influence of one of America's great voluntary health organizations." To the degree that the Association is an organization of this caliber and importance it needs no defense against many of the criticisms that are naturally directed against it, nor do most of its members take them very seriously.

The spirited defense that its leaders find it necessary to make every time a shaft is leveled against the Association seems almost to betray a sense of vulnerability that should by no means exist. So far as the reflections of the *Yale Law Journal* are concerned, if boys could not be boys the nation would be in a sorry plight indeed.

RUDOLPH SCHINDLER AWARD

It is a matter of pride to the medical profession of New England in general, as well as to the gastroscopic cognoscenti of this unique independency, to learn that another New England physician has received the credit due him. This came with the presentation on June 20 of the first Rudolph Schindler award of the American Gastroscopic Society to Dr. Edward B. Benedict, of the Massachusetts General Hospital.

Equally impressive is the fact that the award was made in person by the gastroscopist in whose honor it was named; he had learned of its creation barely in time to dry and hang up his own gastroscopes and make the journey from Los Angeles to San Francisco in time for the presentation.

Rudolph Schindler, one of the first of the scientific peeping Thomases, invented the rigid gastroscope in Germany in 1923, performed his part in developing the Wolf–Schindler flexible gastroscope in 1932 and designed the optical diagnostic esophagoscope in 1948. He came to this country in 1934 as visiting professor of medicine in Chicago, where he served as associate professor from 1937 to 1943, since when he has been clinical professor of medicine at the College of Medical Evangelists in Los Angeles. In 1942 he was a founder and the first president of the American Gastroscopic Society. Although some sort of inference seems unavoidable, gastroscopy is not to be confused with gastronomy.

Dr. Benedict, the recipient of the Schindler award, was the first in this country to use the flexible gastroscope and is the originator of the operating instrument of that name. A gastrophile from the beginning, Dr. Benedict, realizing the risks entailed in rigid gastroscopy, enthusiastically adopted the Wolf–Schindler flexible gastroscope when it appeared in 1932. Step by step he added to his armamentarium esophagoscopy, bronchoscopy and peritoneoscopy, emerging from his various chrysalides as a full-fledged and one of the country's most eminent endoscopists.

Flexible gastroscopy still represents, however, the current zenith of the endoscopist's art, entailing as it does, with those who are as skilled in its employment as Dr. Benedict, the ability to think straight while seeing crooked. Perhaps this peculiar curvilinear capacity of the gastroscope inspired the invention of the new army rifle that shoots around a corner, abolishing forever the idea that straight shooting is one of the indispensable qualities of good marksmanship, whatever its relation to the other facts of life.

TOP-RANKING WOMEN

The American Medical Women's Association, dedicated to the aid and encouragement of women medical students, announces with justifiable pride that women led the graduating classes last June in 7 of the 71 approved schools in the country — of which only 65 had women graduating. For the second consecutive year the Association has presented a cash award of $100 and an Award of Achievement Citation to each of these top-ranking aspirants; in 1953 4 women graduates were thus honored. Six of this year's prize winners achieved this distinction in coeducational institutions, the seventh leading her class at Woman's Medical College of Pennsylvania.

The 7 distinguished graduates are identified as follows: Dr. E. Jean Cowshert, 1 of 2 women in a class of 60 students at the Medical College of the University of Alabama, has been a prize winner from the freshman year, class secretary and treasurer, vice-president of Alpha Omega Alpha and a straight A student.

Dr. Ethel Frances Young, graduating first in a class of 135 students at Northwestern University Medical School, led her class also in the first three years, for which she received the J. Dennis Phi Rho Sigma Scholarship Award.

Dr. Mary Lou Hoover, a member of Alpha Omega Alpha and Alpha Sigma Chi, not only led the graduating class of 100 at the Medical College of Virginia but also has held the highest quality point total for the combined four years as well.

Dr. Martha Wells Usher graduated first in a class of 153 students at the University of Michigan Medical School, 5 per cent of the class being women; Dr. Ray Schwab Greenberg led her classes during the entire four years at the University of Tennessee College of Medicine; Dr. Katharine Emory Spreng, from Oberlin College, the daughter of two physicians and holder of an A.B. degree *summa cum laude*, gradu-

ated first at Western Reserve University School of Medicine, where she was a member of Alpha Omega Alpha, and Dr. Jacqueline Maiorello Mauro, also a member of Alpha Omega Alpha and president of the senior class, graduated *magna cum laude* from the Women's Medical College of Pennsylvania.

Intellectual leadership, the one-time dominant male long since discovered, is no sex-linked character; brains are where you find them.

STATEMENT REGARDING TOBACCO AND HEALTH

THE Tobacco Industry Research Committee reported in July that it had named Timothy V. Hartnett, of Louisville, Kentucky, as its full-time chairman. Mr. Hartnett, who has been in the tobacco industry for forty-five years, retired on June 30 as president of the Brown and Williamson Tobacco Corporation.

Announcing that the tobacco industry is determined to find the answers to the public's questions about smoking and health, Mr. Hartnett stated further that the research will be conducted by recognized medical and scientific organizations and individuals who will report their findings independently. Following this line, the new chairman believes that it is an obligation of the Committee to remind the public of the following essential facts:

1. There is no conclusive scientific proof of a link between smoking and cancer.
2. Medical research points to many possible causes of cancer. Statistics indicating a relationship between smoking and disease could apply with equal force to many other aspects of modern life.
3. Full evaluation of statistical studies now under way is impossible until these studies have been completed, fully documented and exposed to scientific analysis through publication in accepted journals.
4. In their recent preliminary report to the American Medical Association, the American Cancer Society and its statistical research staff placed careful qualifications and limitations on their findings relating to this subject. These qualifying statements should not be overlooked.
5. The millions of people who derive pleasure and satisfaction from smoking can be reassured that every scientific means will be used to get all the facts as soon as possible.

The frank statements of the spokesmen of the tobacco industry can be accepted as guarantees that all evidence for or against the possible damaging effects of tobacco will be carefully appraised and fearlessly publicized. The safety of the public in this respect will obviously be the most important consideration.

Mr. Burt, the manufacturer of the "Pillow-drinking tube," writes us, that, by an improved process, he is enabled to make the article with greater facility and cheapness, and he has therefore reduced the price one half.

Boston M. & S. J., *Sept. 6, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

TOLMAN — Henry Tolman, M.D., of Salem, died on August 5. He was in his seventy-fifth year.

Dr. Tolman received his degree from Harvard Medical School in 1906. He was a fellow of the American Academy of Ophthalmology and Oto-Laryngology, American Medical Association and the American College of Surgeons and a member of the New England Oto-Laryngological Society, Essex South District Medical Society and the staffs of the Beverly, Cable Memorial, North Shore, Babies and Danvers State hospitals.

He is survived by his widow, two daughters and a brother.

BOSTON MEDICAL LIBRARY

HOLMES ON TV

Oliver Wendell Holmes, the hundred and forty-fifth anniversary of whose birth falls on August 29 and who died sixty years ago this fall, will achieve the distinction of a vicarious appearance on television on August 30.

On that day Dr. Holmes and the Boston Medical Library, of which he was the first president, will be incorporated into Louise Morgan's "Shopping Views" over WNAC, from 1 to 1:30.

CORRESPONDENCE

SURGICAL TRAINING FOR THE "GENERALIST"

To the Editor: Dr. Clark, in an article in the July 22 issue of the *Journal*, postulates "two or more years of internship-residency program" for a fairly adequate training of the family doctor.

I should like to suggest that, after the rotating internship, the future "generalist" take one or two years of general surgical training, covering abdominal, urologic, orthopedic, and neurosurgical procedures. Training in gynecology and otolaryngology is also recommended.

Aldous Huxley wrote: "Ce sont les idées qui donnent le courage"—that is, ideas, or perceptions, give courage. Courage is what the general practitioner needs above all.

I remember the night when, after four weeks in practice, I was summoned at midnight to a farmhouse in the backwoods, to visit a boy who, after a motorcycle accident, became drowsy with mounting blood pressure and slowing pulse. I was alarmed but not panicky. When I sent the patient at once to a neurological service and an operation confirmed my diagnosis, my standing in the community was established.

"There is no minor surgery, there are only minor surgeons," said Lahey. Surgical thinking and judgment are more essential for the family doctor than for the surgeon. If the surgeon errs the staff knows it; if the family doctor blunders the community knows it.

Recognition of a true alarm from a false one is difficult but essential. Families resent unnecessary hospitalization. Hesitating to act on "mild" vaginal or oral bleeding, peripheral vascular occlusion or a little indigestion with a tender right lower quadrant invites disaster.

To preserve one's own and the community's respect, many procedures must be undertaken "where the patient lies." Establishment of an airway, aspiration of the chest in pressure pneumothorax, spinal tap, urethral dilatation, adequate initial management of fractures and dislocations and many other technics must be thoroughly learned to be remembered at the moment of need. So must the sequence of orthopedic examination or the technic of adequate cervical biopsy be brought to mind.

The selection of a surgical consultant calls for good judgment. By adding medical knowledge to technical skill, avoiding the knife-happy and the overcautious alike, one can bridge the artificial gap between medical and surgical disciplines and restore unity to the art of healing, giving the patient the best bargain.

GEORGE VASH, M.D.

Chicopee, Massachusetts

FACTORS IN REHABILITATION

To the Editor: The article on Vocational Rehabilitation in the issue of May 27, 1954 is excellent for those with pure and uncomplicated physical disabilities. But are there such persons? Is there an illness whose emotional components, be they causative or resultant, do not enhance the degree of disability? The disability may and often does manifest itself purely as one above and beyond that expected from the simple physical disorder. Then we scratch our heads and can't understand why the subject can't do that simple job.

If he were not *afraid* of failing, if he were not obsessed with *fear* of inadequacy, if he were not *afraid* of his mortality, he would have only the single handicap to overcome. Therefore, an important and indispensable prescription in all cases in which the future means disability should include an evaluation of the emotional capacity of the patient. A psychiatrist is not always necessary for this. The family, the past work record and the former employers can help in determining how much frustration and disappointment the patient can sustain. The physician and social worker can see how depressed and afraid of the future the patient is.

The next job must take these factors into account. The task that is "lighter" physically may be much more strenuous emotionally because it may, for example, mean more responsibility, more compulsiveness and closer contact with people than the personality can cope with. The patient then returns for progressively "lighter" work and eventually is on somebody's "hand-out" payroll for life. The diagnosis is now: "chronic compensititis" due to emotional maladjustment precipitated by relatively minor physical disorder.

JOSEPH I. BERNSTEIN
Captain, MC

ST. VINCENT HOSPITAL

To the Editor: The following news about St. Vincent Hospital in Worcester, Massachusetts, will be of interest to many of your readers.

St. Vincent Hospital is affiliated with the Georgetown University Medical Center in Washington, D. C., with Dr. John F. Stapleton, as full-time director of medical education; Dr. Stapleton is instructor in medicine at Georgetown University School of Medicine.

Dr. Harold Jeghers, director, Department of Medicine, Georgetown University Medical Center, has been appointed consultant in medical education on the staff of St. Vincent. Dr. Francis Forster, dean of Georgetown Medical School, will be serving as consultant in neuropsychiatry. Other heads of department at the University are serving in comparable capacity as consultants.

The affiliation is similar to that which has been successfully functioning for several years between Georgetown and the Mercy Hospital of Buffalo, New York, as well as St. Mary's Hospital of Rochester, New York. The program is designed to improve the level of medical education in the participating hospital at the postgraduate as well as the graduate level.

JOHN F. STAPLETON, M.D.
Director of Medical Education

Worcester, Massachusetts

NIGHT SWEATS

To the Editor: In many hospitals it seems that the recording of patients' histories is slighted for the hasty resort to laboratory aids for diagnosis or experimental and multiple technics of therapy.

A symptom, less often elicited nowadays when clinical thermometers are in such common use but nevertheless quite worth noting because of its traditional value, is that of night sweats. Night sweats are more impressive than their counterpart of chilly sensations or vague aches that occur during the day, when the prospective patient is less apt to notice them. A fact that is overlooked by physicians as well as laymen is that a fever may escape detection because the rise in temperature may not occur until 10 or 11 p.m., when the reading is hardly ever taken. Neither the patient nor a member of the family should fail to discover the occurrence of night sweats.

GILBERT W. HAIOH, M.D.

Worcester, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Kinsey's Myth of Female Sexuality: The medical facts. By Edmund Bergler, M.D.; and William S. Kroger, M.D., associate clinical professor of gynecology, Chicago Medical School. 8°, cloth, 200 pp. New York: Grune and Stratton, 1954. $3.75.

The two authors, one a psychiatrist, the other a gynecologist, seek to prove that the nonmedical approach has led Professor Kinsey astray in his conclusions stated in his recent book on female sexuality.

You and Your Skin. By Norman R. Goldsmith, M.D., dermatologist, St. Joseph's Hospital, Lancaster, Pennsylvania. 8°, cloth, 148 pp., with 5 illustrations and frontispiece. Springfield, Illinois: Charles C Thomas, 1953. $3.75.

This small book on the skin, its care and its diseases is intended primarily for the patient but should be of value to the general practitioner. Considerable space is given to allergic conditions, cosmetics, infections and insect bites. There are chapters on the hair and nails. The text is written in an easy style in everyday English. There is a good index, and the publishing is excellent.

The Chest: A handbook of roentgen diagnosis. By Leo G. Rigler, M.D., professor of radiology and chief, Department of Radiology, University of Minnesota Medical School. Second edition. 8°, cloth, 380 pp., with 338 illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $8.00.

This book, first published in 1946, has been revised and brought up to date. Considerable material has been added to the text, including newer terminology, numerical designation of the bronchi, recent technics in bronchography and early diagnosis of lung tumors. Illustrations have been added, and some replaced. The book is a small atlas; the illustrations are excellent. There is a short list of references and a good index.

Diabetic Care in Pictures: Simplified statements with illustrations prepared for the use of the patient. By Helen Rosenthal, B.S.; and Joseph Rosenthal, M.D., physician-in-charge, Diabetes Clinic, Boston Dispensary, assistant professor of medicine, Tufts College Medical School, and member, associate staff, Joseph H. Pratt Diagnostic Hospital, New England Medical Center. Second edition. 8°, cloth, 164 pp., with 128 illustrations, prepared under the direction of the authors. Philadelphia: J. B. Lippincott Company, 1953. $3.00.

The first edition of this picture book was issued in 1946. In this second edition pictures have been added on the food exchanges of the carbohydrates, proteins and fats. A new exchange sheet on dairy products, a comprehensive table of food values and new information on the insulin preparations and detailed instructions for their administration have been included. There is a good index; the publishing is excellent, and the price is within the means of patients.

Pelvic Relaxations and Herniations. By James M. Wilson, M.D., assistant professor of gynecology and obstetrics, Medical College of South Carolina. 8°, cloth, 64 pp., with 35 illustrations by Elon Henry Clark, artist and professor of medical art and illustration, Duke University School of Medicine. Springfield, Illinois: Charles C Thomas, 1954. $2.75. (Publication No. 203, *American Lecture Series.*)

This book, written for students, illustrates the pelvic anatomy from the clinical aspect and shows the changes that occur with pelvic relaxation. The various types of hernia and rectocele, cystocele, urethrocele and prolapse of the uterus and of the vaginal wall after hysterectomy are described and illustrated. The indications for surgery and the principles of repair are discussed, and there is a chapter on episiotomy. Lists of references are appended to the chapters, and there is an index.

Coal Tar and Cutaneous Carcinogenesis in Industry. By Frank C. Combes, M.D., professor of dermatology and syphilology, New York University Post-Graduate Medical School, and director of dermatology and syphililogy, Bellevue Hospital, New York City. 8°, cloth, 76 pp., with 25 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $2.75. (Publication No. 189, *American Lecture Series.*)

This small book is written principally for the dermatologist and the industrial physician. A large number of chemical compounds are carcinogenic, of which more than 300 are capable of inducing cancer in laboratory animals and about 35 are capable of inducing benign tumors. The author discusses the carcinogenic nature of certain fractions of coal tar as they concern workmen in industry. There are chapters on dermatergoses from coal tar, petroleum cancer and advices for control of "tar cancer." This important monograph is well illustrated. There is a bibliography of 105 references and a good index.

The Effect of ACTH and Cortisone Upon Infection and Resistance: Symposium held at the New York Academy of Medicine, March 27 and 28, 1952. Edited by Gregory Shwartzman, M.D. 8°, cloth, 204 pp., with illustrations and tables. New York: Columbia University Press, 1953. $5.50.

This symposium was held under the auspices of the Section on Microbiology (established in 1947) of the New York Academy of Medicine. The 13 papers read concerned the effect of the two hormones on various infectious diseases and on the action of hormones in general. Thirty-one authorities participated in the discussions. Lists of references are appended to the chapters, and the publishing is excellent. There is a table of contents but no index. It is suggested that in the future indexes be prepared for the symposia. The complete series should be in all medical libraries.

A Handbook on Diseases of Children. Including Dietetics and the Common Fevers. By Bruce Williamson, M.D. (Edin.), F.R.C.P. Lond., physician, Children's Department, Royal Northern Hospital, London, physician, Children's Hospital, Northaw, physician, Prince of Wales General Hospital, London, physician, Barnet General Hospital, physician, Enfield War Memorial Hospital, and lecturer, North London Post-Graduate Institute. Seventh edition. 12°, cloth, 467 pp., with 102 illustrations. London: E. and S. Livingstone, Limited. 1953. $5.00.

This standard handbook, first published in 1933, has been thoroughly revised, and much material has been added to the text. There is an extensive index, and the publishing is good.

Medical Treatment of Disease. By Henry A. Christian, A.M., M.D., LL.D., Sc.D.(Hon.), M.A.C.P., Hon. F.R.C.P. Can., D.S.M.(A.M.A.); Dale G. Friend, M.S., M.D., colonel, Medical Corps, A.U.S., Southwest Pacific and European Theaters, World War II, associate in medicine, Harvard Medical School, senior associate in medicine, Peter Bent Brigham Hospital, clinical pharmacologist, Peter Bent Brigham Hospital, consultant in medicine, Sturdy Memorial Hospital, and consultant in medicine, Veterans Administration; and Maurice A. Schnitker, M.D., lieutenant colonel, Medical Corps, A.U.S., medical consultant, Pacific Theater, World War II, director of medicine, St. Vincent's Hospital, senior attending physician, Toledo Hospital, chief of staff, Maumee Valley Hospital, and consultant, Toledo State and Robinwood hospitals, Toledo, Ohio. 8°, cloth, 965 pp. New York: Oxford University Press, 1953. $25.00. (Vol. 8 of *The Oxford Medicine.*)

This new volume in the Oxford series is written primarily for the physician and internist. The infections and diseases of the various systems of the body are well covered. Lists of selected references are appended to the chapters, and there is a good index. The book furnishes up-to-date information and should prove valuable to the general physician. Dr. Christian died while the book was in press.

Rat Quality: A consideration of heredity, diet and disease. Proceedings of the Symposium held at Columbia University, College of Physicians and Surgeons, New York, January 31, 1952. 8°, paper, 138 pp., with illustrations. New York: National Vitamin Foundation, Incorporated, November, 1953. $2.50.

Nine persons took part in this symposium on the rat as a laboratory animal.

Parsons' Diseases of the Eye. By Sir Stewart Duke-Elder, K.C.V.O., Ph.D., D.Sc., LL.D., M.D., F.R.C.S., surgeon-oculist to the Queen, director of Research, Institute of Ophthalmology, University of London, ophthalmic surgeon, St. George's Hospital, London, and consulting ophthalmic surgeon, Moorfields Hospital. Twelfth edition. 8°, cloth, 606 pp., with 22 colored plates and 465 text figures. New York: Macmillan Company, 1954. $8.00.

The authors have made a thorough revision of this standard manual for students and general practitioners. Many sections have been rewritten, especially those on the etiology of uveitis, the retinopathies, glaucoma and the ocular manifestations of general disease. The greatest changes are in the field of treatment, and much of therapeutics has been changed. A chapter has been added on the antibiotics and hormones. In surgery descriptions of cyclodiathermy and keratoplasty have been included. There is a good index, and the publishing is excellent.

Side Effects of Drugs. By L. Meyler, consulting physician at Groningen (Netherlands). Translated by Ph. Vuijsje and W. Mulhall. Corbet, Amsterdam. 8°, cloth, 268 pp. New York: Elsevier Publishing Company, 1952. $5.50.

The author has endeavored to collect all the known facts concerning the side effects of drugs. The material is arranged by classes of therapeutic agents, and extensive lists of references are appended to the chapters. There is a good index; the book should prove valuable as a reference source.

Textbook of Physiology and Biochemistry. By George H. Bell, B.Sc., M.D. (Glasg.), F.R.F.P.S.G., F.R.S.E., professor of physiology in the University of St. Andrews at University College, Dundee; J. Normal Davidson, M.D., D.Sc., (Edin.), F.R.F.P.S.G., F.R.I.C., F.R.S.E., Gardiner Professor of Physiological Chemistry in the University of Glasgow; and Harold Scarborough, M.B., Ph.D. (Edin.), F.R.C.P.E., professor of medicine in the Welsh National School of Medicine of the University of Wales and director of the

Medical Unit in the Royal Infirmary, Cardiff. With a foreword by Robert C. Garry, M.B., D.Sc. (Glasg.), F.R.F.P.S.G., F.R.S.E., Regius Professor of Physiology in the University of Glasgow. Second edition. 8°, cloth, 1002 pp., with 55 illustrations. Edinburgh: E. and S. Livingstone, Limited, 1953. $10.00. (Distributed by Williams and Wilkins, Baltimore, Maryland.)

The first edition of this new textbook, published in 1950, was reprinted in 1952. The need for a second edition in three years speaks well for its soundness and popularity. The authors have brought their text up to date. Lists of references are appended to the 56 chapters, and there is a comprehensive index. The publishing is excellent. The book, expressing the British point of view, should be in collections on the subject.

Dermatologic Medications. By Marguerite Rush Lerner, M.D., resident, Department of Dermatology, and Aaron Bunsen Lerner, M.D., Ph.D., associate professor of dermatology, University of Oregon Medical School. 12°, paper, 183 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $3.50.

This formulary is divided into 2 parts: therapeutic agents and treatment regimens. In the first, which is arranged alphabetically by subjects, the common agents of greatest therapeutic values are described. The second part gives regimens for skin disorders that require progressional or simultaneous types of treatment. There is a bibliography and a good index; the book is well published.

Children for the Childless: A concise explanation of the medical, scientific and legal facts about conception, fertility, sterility, heredity, and adoption. Edited by Morris Fishbein, M.D. 8°, cloth, 223 pp., with illustrations. New York: Doubleday and Company, Incorporated, 1954. $2.95.

Written for the layman, this book is the joint work of 9 authorities. It presents a concise explanation of the medical, scientific and legal facts about conception, fertility, sterility, heredity and adoption.

The Jealous Child. By Edward Podolsky, M.D., Department of Psychiatry, Kings County Hospital, Brooklyn, New York. 8°, cloth, 147 pp. New York: Philosophical Library, 1954. $3.75.

The author discusses the various conditions, physical, emotional, social and economic, that may result in jealousy in a child and endeavors to point out what may be done for the child.

Practical Electrocardiography. By Henry J. L. Marriott, M.D., associate professor of medicine, University of Maryland School of Medicine, and assistant cardiologist, Mercy Hospital, Baltimore. Illustrated by Marcie Ethridge Perry. 8°, cloth, 171 pp., with illustrations. Baltimore, Maryland: Williams and Wilkins, 1954.

For a number of years the author has been teaching fourth-year medical students a comparatively easy technic of interpreting electrocardiograms. He has not found a book that he could recommend to his students, and he has therefore written this manual in a simple but comprehensive manner. It emphasizes the simplicities rather than the complexities, presents only the electrophysiologic concepts that make interpretation more intelligible without the burden of unnecessary detail, covers all diagnostically important electrocardiographic patterns and provides adequate illustrations in close proximity to the descriptive text. There are indexes of illustrations and subjects, and the publishing is excellent.

Lectures on the Thyroid. By J. H. Means, M.D., Jackson Professor of Clinical Medicine emeritus, Harvard University, and formerly, chief, Medical Services, Massachusetts General Hospital, and physician, Massachusetts Institute of Technology. 8°, cloth, 113 pp., with illustrations. Cambridge, Massachusetts: Harvard University Press, 1954. $3.00.

The 5 lectures in this volume were delivered at various places from June, 1949, to April, 1953, and published in various medical periodicals. They are brought together for convenience and reflect the author's views on the subject. The first 4 lectures have been edited and brought up to date. There are lists of references for each lecture, and a general index has been provided for the series.

Methods in Medical Research. Vol. 6. J. Murray Steele, editor-in-chief. Antonio Ciocco, Ray G. Daggs, Donald Mainland and Arnold Lazarow, editors. 8°, cloth, 271 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1954. $7.00.

This volume in an important series is the joint work of 28 contributors and reviewers. The text is divided into 4 sections: methods in the study of human genetics; technics of environmental medical research; statistics in medical research; and design and construction of metabolism cages. Short lists of references are appended to the chapters, and there is a good index. The series should be in all medical libraries.

Global Epidemiology: A geography of disease and sanitation. By James Stevens Simmons, M.D., Ph.D., Dr. P.H., Sc.D. (Hon.), Brigadier General, United States Army, retired; dean and professor of Public Health, Harvard University School of Public Health; and Tom F. Whayne, A.B., M.D., M.P.H., Dr. P.H., Colonel, M.C., United States Army, chief, Preventive Medicine Division, Office of the Surgeon General, United States Army; and Gaylord W. Anderson, M.D., Dr. P.H., Mayo Professor of Public Health and director, School of Public Health, University of Minnesota; and Harold Maclachlan Horack, M.D., member of staff, Department of Medicine and Section of Cardiology, Ochsner Clinic, New Orleans, and instructor in medicine, Tulane University of Louisiana School of Medicine. Associate author Ruth Alida Thomas, B.A., A.M., M.P.H., research associate, School of Public Health, University of Minnesota, and instructor, Department of Tropical Public Health, Harvard School of Public Health. Vol. 3. *The Near and Middle East.* 4°, cloth, 357 pp., with illustrations. Philadelphia: J. B. Lippincott Co., 1954. $12.00.

This volume, part of a series of 5, of which those on India, the Far East and the Pacific area and Africa have already been published, concerns the Near and Middle East bordering on the U.S.S.R. It discusses the public-health problems of 17 geographic areas of the eastern Mediterranean region, the Arabian Peninsula and southwestern Asia, and gives a brief but comprehensive summary of the disease hazards of these countries, indicating the major factors, including medical, that affect the health and well-being of the inhabitants. The text is arranged by countries or regions, and lists of references are appended to each section. There is an index, and the publishing is excellent. The nongloss paper, type and printing are very good and make reading a pleasure. The set is a fundamental reference source.

Aportación de la escuela española a la técnica endobronquial: Análisis cronológico y doctrinal. By Dr. S. Garcia-Vicente. Conferencia pronunciada en la Real Academia Nacional de Medicina. 8°, paper, 43 pp., with illustrations. Madrid, 1953. Free.

The author discusses his method of pulmonary lavage for therapeutic purposes, first described by him in 1928. There are résumés in Spanish, French, English and German. The English translation is very poor. There is a bibliography of the author's 18 articles on this subject and a list of 50 titles by other persons.

Music Therapy. Edited by Edward Podolsky, M.D., Department of Psychiatry, Kings County Hospital, Brooklyn, New York. 8°, cloth, 335 pp., with illustrations. New York: Philosophical Library, 1954. $6.00.

This book is the joint work of 38 contributors, who discuss music therapy in a variety of mental, emotional and physical conditions. This type of treatment has become established in a number of clinics and hospitals throughout the world. The introduction presents a short history of the subject, and a list of references concludes the text. The lack of an index detracts from the reference value of the book.

Medical Psychology. By Paul Schilder. Translated and edited by David Rapaport, Austen Riggs Center, Incorporated. Stockbridge, Massachusetts. 8°, cloth, 428 pp. New York: International Universities Press, Incorporated, 1953. $7.50.

"The Pre-Adolescent Exceptional Child": Proceedings of the 35th conference of the Child Research Clinic of The Woods Schools held in the Bellevue-Stratford Hotel, Philadelphia, Saturday, May 23, 1953. 8°, paper, 67 pp. Langhorne, Pennsylvania. Free.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

The next meeting of the New England Pediatric Society will be held in the Jimmy Fund Auditorium, Boston, September 22, beginning at 11 a.m. A clinicopathological conference will be held at noon, followed by the scientific session until 5 p.m. and the evening meeting at 7:30 p.m.

McINTYRE–SARANAC CONFERENCE

A conference on silicosis and occupational chest diseases, jointly sponsored by the McIntyre Research Foundation of Toronto, Canada, and the Saranac Laboratory of Saranac Lake, New York, will be held in the town hall, Saranac Lake, February 7-9, 1955.

Dr. Anthony J. Lanza, professor, emeritus, of industrial medicine, New York University–Bellevue Medical Center, will be the chairman. Physicians, scientists, and businessmen concerned with the problems of occupational chest diseases are invited. Further information may be obtained from Norman R. Sturgis, Jr., Saranac Laboratory, Saranac Lake, New York.

NATIONAL VITAMIN FOUNDATION SYMPOSIUM

The National Vitamin Foundation will sponsor a symposium on the nutritional aspects of blood formation in the auditorium of the University of Cincinnati College of Medicine on October 22.

The chairmen will be Drs. Richard W. Vilter and M. A. Blankerhorn. All interested physicians and scientists are invited.

AMERICAN CANCER SOCIETY CLINICAL FELLOWSHIPS

The American Cancer Society announces the continuation of the clinical-fellowship grants, available primarily to teaching institutions approved by the Council on Medical Education and Hospitals of the American Medical Association. A stipend of $3600 will be awarded for one year. Individual applicants should apply directly to the institutions where such fellowships are available. A list of such institutions may be obtained from the National Office of the American Cancer Society. Applications must be submitted through the institution in which the work will be done to Dr. Brewster S. Miller, 47 Beaver Street, New York 4, New York, before September 15.

LIFE INSURANCE MEDICAL RESEARCH FUND

Research fellowships and grants offered by the Life Insurance Medical Research Fund are as follows:

Postdoctoral research fellowships for work on cardiovascular function and diseases or related fundamental problems. The minimum salary will be $3500, with allowances for dependents and necessary travel. Applications must be received before October 29.

Grants to institutions for research in cardiovascular problems and physiologic, biochemical and other broadly related basic work and clinical research. Applications must be received before November 15.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, New York.

CONGRESS OF CARDIOLOGY

At the second International Congress of Cardiology, to be held in Washington, D.C., September 12 to 15, Dr. Robert E. Gross, of the Boston Children's Hospital, Dr. Samuel A. Levine, of Peter Bent Brigham Hospital, and Drs. Howard B. Sprague and Paul D. White, of Massachusetts General Hospital, will preside as chairmen of various panels. Dr. White is presiding officer of the Congress.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER, 1954–MAY, 1955. Venereal Disease Research Laboratory Courses. Page 285, issue of August 12.

SEPTEMBER 7–28. Consultation Clinics for Crippled Children in Massachusetts. Page 362, issue of August 26.

SEPTEMBER 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

SEPTEMBER 6–11. University of Illinois College of Medicine. Annual Assembly in Otolaryngology. Page 1092, issue of June 24.

SEPTEMBER 6–11. American Congress of Physical Medicine and Rehabilitation. Page 246, issue of August 5.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Washington, D. C. Notice above.

SEPTEMBER 13–15. American Association of Blood Banks. Page 968, issue of June 3.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Washington, D. C.

SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.

SEPTEMBER 22–24. Mississippi Valley Medical Society. Page 246, issue of August 5.

SEPTEMBER 23–25. Industrial Health Conference. Page 364, issue of August 26.

SEPTEMBER 24. American Medical Writers' Association. Page 246, issue of August 5.

SEPTEMBER 30–OCTOBER 2. Canadian Society for the Study of Fertility. Page 285, issue of August 12.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Page 1092, issue of June 24.

OCTOBER 8 and 9. Academy of Psychosomatic Medicine. Page 748, issue of April 29.

OCTOBER 11–15. American College of Physicians Course. Page 44, issue of July 1.

OCTOBER 16–22. American Occupational Therapy Association. Page 1092, issue of June 24.

OCTOBER 18–29. New York Academy of Medicine Graduate Fortnight. Page 44, issue of July 1.

OCTOBER 22. National Vitamin Foundation Symposium. Notice above.

OCTOBER 25–27. New England Postgraduate Assembly. Hotel Statler, Boston.

OCTOBER 25–30. Course in Care of Atomic Casualties. Page 285, issue of August 12.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

OCTOBER 27–29. International Symposium on the Hypophyseal Growth Hormone. Page 1092, issue of June 24.

OCTOBER 31–NOVEMBER 4. American Institute of Dental Medicine. Page 968, issue of June 3.

NOVEMBER, 1954–MAY, 1955. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

NOVEMBER 3–5. National Society for Crippled Children and Adults. Page 44, issue of July 1.

NOVEMBER 12 and 13. Inter-Society Cytology Council. Page 968, issue of June 3.

NOVEMBER 15–26. Laboratory Diagnosis of Tuberculosis. (Course.) Page 246, issue of August 5.

DECEMBER 5. American Academy of Dental Medicine. Page 1092, issue of June 24.

DECEMBER 8. New England Pediatric Society. Page 968, issue of June 3.

DECEMBER 13–17. Congress of Obstetrics and Gynecology. Page 748, issue of April 29.

JANUARY 10–15, 1955. Course in Care of Atomic Casualties. Page 285, issue of August 12.

FEBRUARY 7–9. McIntyre-Saranac Conference. Notice above.

MARCH 7–12, 1955. Course in Care of Atomic Casualties. Page 285, issue of August 12.

MAY 4 and 5, 1955. American Psychosomatic Society. Page 286, issue of August 12.

JUNE 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 9

THURSDAY, SEPTEMBER 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00–10:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*10:00–11:00 a.m. Surgical Rounds. 5th floor teaching unit, Beth Israel Hospital.

(Notices concluded on page xvii)